Alcohol and cardiovascular disease: A critical review of scientific evidence for protective versus harmful effects

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Executive Summary

Background and objectives

Many observational and some experimental studies have long suggested an association between moderate use of alcohol and a reduced risk of cardiovascular diseases (CVDs). Because CVDs are a leading cause of premature death, especially in economically developed countries, the existence or not of such benefits have major implications for national drinking guidelines and estimates of alcohol's toll on global health. The aim of this report is to review the current state of evidence on this question, drawing on available published systematic reviews and meta-analyses (SRMAs) that include studies with experimental, genetic (Mendelian Randomisation (MR)) and/or observational designs.

Methodology

The scholarly databases PubMed, Cochrane Library, Epistemonikos, International HTA, JBI, PsycNet and Web of Science were searched for studies on alcohol and CVD published between 2014 and 2024. Outcomes of interest included incidence of disease, mortality, key risk factors (high blood pressure, blood sugar and arterial stiffness) and indirect biomarkers of cardiac risk (e.g. HDL and LDL cholesterol). Specific disease types included in the search were: ischaemic heart disease (IHD, including myocardial infarction or MI), ischaemic stroke, haemorrhagic stroke, atrial fibrillation (AF), heart failure, hypertension and type II diabetes. Risk of bias was broadly assessed, firstly in terms of type of study design with greater weight given to randomised controlled trials, other experimental designs with control observations, then genetic (MR) studies and finally, with less weight given, to observational studies. For observational studies, risk of lifetime selection bias was a particular focus e.g. whether the non-drinking comparison group is likely to include people who have stopped or cut down due to ill health.

Results

A total of 379 articles were retrieved from initial searches. After exclusions for eligibility, duplicates and inclusion of additional earlier SRMAs from citation searching, 46 unique SRMAs were included plus two umbrella reviews. The majority considered outcomes of disease incidence and/or mortality (n=31), 12 SRMAs addressed key risk factors for CVD and three examined cardiac biomarkers.

(i) Studies with CVD-related incidence or mortality outcomes

We identified one randomised controlled trial (RCT) relating alcohol use to CVD related incidence (Voskoboinik et al., 2020) and none with mortality outcomes. Voskoboinik et al. (2020) demonstrated a significant reduction in rates of relapse among mostly moderate drinking individuals with a recent diagnosis of atrial fibrillation (AF) after being randomly assigned to a successful abstinence intervention. However, two SRMAs were identified of genetic studies using MR methodology which incorporates some strengths of an RCT and by reducing or even eliminating confounding, exposure misclassification, and reverse causation. These reviews found no evidence for health benefits of low to moderate alcohol consumption in relation to ischaemic heart disease, unspecified stroke, atrial fibrillation, hypertension, heart failure or unspecified CVD-related illnesses.

Observational studies are more numerous but are highly susceptible to the effects of selection bias, reverse causation, under-reporting of alcohol use, residual confounding and exposure misclassification (Wallach et al., 2020). Authors of identified SRMAs on observational studies mostly concluded that low to moderate alcohol use was associated with reduced risk of some CVD-related illnesses, in particular: IHD (including MI), ischaemic stroke, heart failure and unspecified CVD. Most SRMAs took no or inadequate account of systematic bias affecting the abstainer reference groups, so these conclusions are likely based on underestimated risks from alcohol use. However, Zhao et al. (2017) applied a strict criterion for lifetime abstention and mitigated risk of lifetime systematic bias with an analysis of younger cohorts followed up to old age. They found no significant protection against IHD for consumption of up to two drinks per day. Some other SRMAs, both for IHD and other outcomes, made partial attempts to reduce selection bias and some of these still concluded possible protective effects in relation to IHD, ischaemic stroke and heart failure. It is clearly necessary for more studies as well as SRMAs on alcohol and CVD-related illness to be conducted in which more effective steps are taken to reduce lifetime selection bias.

In relation to other CVD-related conditions, there was no evidence in observational or other types of study for protection against haemorrhagic stroke, hypertension and atrial fibrillation. Because lifetime selection biases tend to make non-drinking comparison groups less healthy, estimates of the impact of low to moderate drinking on disease incidence and mortality will also have been underestimated in these studies.

An umbrella review of 25 systematic reviews and meta-analyses of studies on alcohol and all-cause mortality (Sarich et al., 2024) identified only five which had taken steps to minimise

lifetime selection bias. The only one of these assessed as having a low risk of bias found no significant protective effects for low to moderate alcohol consumption.

In summary, studies with stronger research designs find no evidence of protective effects of low to moderate alcohol use in relation to CVD incidence or mortality. By contrast, there is strong and consistent evidence across multiple study designs and disease outcomes for negative effects from higher levels of alcohol consumption i.e. increased risk of CVD illness and mortality.

(ii) Studies of alcohol use and CVD risk factors

Evidence from experimental (short and longer-term outcomes), genetic (MR) and observational studies support the conclusions that a) there is a positive association between alcohol use and higher blood pressure overall, and b) there are no protective effects at low levels of consumption. Furthermore, experimental trials with interventions to reduce drinking also show reductions in blood pressure among those who had previously been drinking two or more drinks daily.

Some evidence for limited health benefits in relation to glucose control and type II diabetes was provided by SRMAs for low to moderate alcohol use in short-term experimental and some observational studies. The observational studies for diabetes suggested no association for men but some beneficial associations for women who were overweight or obese. The most recent relevant SRMA (Schrieks et al., 2015) took some partial steps to reduce lifetime selection bias but the review was restricted to short-term outcomes among individuals without diabetes. This SRMA also declared receipt of alcohol industry funding. However, a unique two year-long RCT involving the administration of wine or water with an evening meal to an Israeli cohort with type II diabetes found no evidence for significant improvement in haemoglobin levels in the wine groups as measured by A1c, the most reliable indicator of type II diabetes severity (Gepner et al., 2015). The MR genetic studies available also found no protective effects for alcohol and type II diabetes.

Stronger study designs, namely experimental and genetic studies, mostly found negative effects of low to moderate alcohol use on the associated risk factor of arterial stiffness (otherwise known as endothelial functioning). Some studies included in these SRMAs noted that grape juice and/or de-alcoholised red wine were associated with similar or improved outcomes compared with wine. Observational studies, mostly cross-sectional, tended to find

beneficial associations for endothelial function. However, these took no account of lifetime selection bias.

We conclude there is relatively strong evidence, across multiple types of study, against the hypothesis that low to moderate alcohol use has beneficial effects in relation to blood pressure, blood glucose control or arterial stiffness. There was strong and consistent evidence across multiple study designs for adverse effects from higher levels of alcohol consumption on blood pressure, blood glucose control and arterial stiffness.

(iii) Studies of alcohol use and indirect CVD biomarkers

SRMAs of the many experimental and observational studies on these indirect markers of CVD risk found positive associations between alcohol and "good" cholesterol (HDL) and no or inconsistent results for "bad" cholesterol (LDL). HDL, however, is no longer widely accepted as a reliable predictor of future heart disease. A comprehensive SRMA by Brien et al. (2011) found evidence of potential benefits for only two out of a further 11 cardiac biomarkers, namely adiponectin and fibrinogen. However, there is also evidence that equivalent or greater benefits can be gained from consuming some kinds of fruit, particularly grapes (e.g. Weaver et al., 2021). We conclude this area of research provides weak and inconsistent evidence for beneficial effects for two out of 12 possible indicators of future heart health. There was strong and consistent evidence across multiple study designs for adverse effects from higher levels of alcohol consumption on a range of cardiac biomarkers.

Conclusions

There are now strong grounds for scepticism about the hypothesis that alcohol use in moderation can protect against heart disease. The classic J-shaped curve used to describe the fall below a relative risk of 1.0 and rise of mortality risk with level of alcohol use is absent in genetic (MR) and observational studies with stronger research designs. Furthermore, the widespread failure of observational studies (and many SRMAs of these) to take account of lifetime selection bias means that the extent of disease and mortality risk from alcohol use at any level is likely underestimated.

A new wave of research in this area using MR methodologies consistently finds either no association between alcohol use and CVD risk for some conditions (e.g. IHD) or positive linear risk increases in CVD risk for others (e.g. strokes, hypertension). Experimental studies indicate that even low to moderate levels of alcohol use can raise CVD risk through increased blood pressure and arterial stiffness. Evidence for an association between low

dose alcohol use and improved blood glucose control was limited to short-term studies with nondiabetics and observational studies with no adjustment for selection bias. The single strongest study, a two year long RCT, found no significant impact on either fasting blood sugar or haemoglobin A1c (Gepner et al., 2015).

At higher levels of alcohol consumption there is consistent evidence of adverse effects on biomarkers, risk factors and the incidence of CVD.

Recommendations for future research

1. More high quality studies are needed using genetic MR methodologies and which conduct analyses to test for potential "non-linear" e.g. J-shaped risk relationships. In particular, we suggest more studies on alcohol and novel biomarkers (e.g. proteomics and metabolomics), combined with genetic methodologies, to understand the potential diverse biological mechanistic pathways through which alcohol may affect CVD risk.

2. More observational studies with prospective designs are needed in which strict measures are taken to reduce lifetime selection biases that are prevalent in the existing literature e.g. strict defining of lifetime abstainers, recruiting younger cohorts (<50 years), ascertaining lifetime drinking patterns more precisely and/or using long term occasional drinkers as the reference (e.g. Ortolá et al., 2024).

3. We recommend the development of further, innovative RCT trials involving daily low-dose alcohol administration versus no alcohol control conditions and/or intervention trials aimed at reducing consumption of light to moderate drinkers (e.g. Voskoboinik et al., 2020). These could assess intermediate outcomes (blood sugar, blood pressure, endothelial function) and, ideally, also longer term morbidity and mortality.

4. If cardio-protection is assumed in estimates of the Global Burden of Disease from alcohol, harms and benefits attributable to alcohol should be estimated and reported separately to avoid masking the adverse effects of alcohol on health.

Introduction

The idea that moderate alcohol use might have significant benefits for heart health has a long and, at times, controversial history. In this review we will attempt to summarise the current scientific evidence regarding the implications of alcohol use for lifetime risk of cardiovascular diseases (CVDs). We will present findings from recent systematic reviews and meta-analyses (SRMAs) on this topic, taking careful account of study quality and risk of bias.

This issue has global significance given the widespread use of alcohol, especially in middle- and high-income countries. At 9.2 litres per person aged 15+ per year, Europe has the highest alcohol consumption of any World Health Organization (WHO) global region, with 62.4% of the adult population reporting use of alcohol in the past year (WHO Global Status Report on Alcohol, 2024).

Some respected scientific and public health bodies report evidence that, at mostly lower doses per day, alcohol can reduce the risk of ischaemic heart disease (IHD), ischaemic stroke and type II diabetes (Griswold et al., 2018; WHO, 2024). The upper levels of alcohol use at which protective effects have been estimated vary widely between different expert groups. At one extreme, the influential 2020 Global Burden of Disease group estimated this to apply for IHD prevention at up to *nine alcoholic drinks per day* (Bryazka et al., 2022) and at the other end, the group responsible for developing the recent Canadian Guidance and Alcohol and Health estimated marginal benefits at up to just *one drink per day* (Levesque et al., 2023). Such widely varying estimates have very different implications, both for advice to consumers and for estimates of alcohol's impact on global health.

Despite these high-level endorsements, scientific criticisms of the alcohol and health benefit hypothesis have mounted over the past two decades. Naimi et al. (2005) demonstrated how moderate drinkers fared significantly better on 27/30 risk/protection factors for heart health compared with abstainers in ways unrelated to their alcohol use e.g. they had better access to healthcare, exercised more, had lower BMIs, higher incomes and better diets. Fillmore et al. (2006) reported an SRMA in which most studies supporting the health benefit hypothesis contained a systematic bias that led to an exaggeration of illnesses in people categorised as abstainers thus making drinkers appear healthier by comparison. Fekjaer (2013) reported a range of improbable or impossible health benefits claimed for moderate alcohol use reported in published studies e.g. protection against deafness, the common cold, hip fractures and liver cirrhosis. The implication being that statistical error lay behind these findings. More

recently, Ortolá et al. (2019) reported that apparent health benefits for elderly moderate drinkers vanished when lifetime drinking patterns were assessed rather than a much later snapshot. Zhao et al. (2023) demonstrated that when statistical adjustments for study design and population type health were applied in meta-analysis, benefits for moderate drinkers were no longer significant.

High-profile international health bodies have also recently taken a public stance against recommending moderate alcohol use to improve health and well-being. WHO (2023) declared "no level of alcohol consumption is safe for our health". The World Heart Federation (2022) advised that the science supporting health benefits from alcohol was questionable and cardiologists should not encourage alcohol use to improve heart health.

Cardiovascular-related conditions reviewed

In preparing the present literature review, we have conducted searches of relevant scholarly databases to extract systematic reviews and meta-analyses which compile and synthesise evidence regarding the effects of alcohol use and the following types of cardiovascular outcome:

- Ischaemic heart disease (including myocardial infarction) (IHD/MI)
- Ischaemic stroke
- Haemorrhagic stroke
- Cerebrovascular accident
- Atrial fibrillation (AF)
- Atrial flutter
- Heart failure
- Peripheral artery disease (PAD)
- Cardiovascular disease (CVD, *unspecified*)
- Hypertension
- Type 2 diabetes

We will also briefly consider results from prospective studies examining the association between level of alcohol use and risk of death from all causes. While as many as 95% of deaths globally are unrelated to alcohol use (WHO, 2024), there are many published studies on alcohol and all-cause mortality and they can shed light on the potential benefits and risks of alcohol use. They also have the advantage of a discrete and reliably documented outcome (a death) and do not, therefore, suffer from potential problems with competing causes of death which are rarely taken account of in studies with specific causes of death

such as cardiovascular diseases. Furthermore, the famous J-shaped curve that illustrates the idea that alcohol has health benefits is based on all-cause mortality studies.

Strength of study design

It is widely accepted in health research that randomised controlled trials (RCT) provide the strongest evidence of causal associations between an exposure variable (e.g. alcohol consumption) and a disease outcome (e.g. IHD). To date, no RCT on alcohol and health using morbidity and/or mortality outcomes has been conducted. The expense and logistics of such a study would be considerable. A recent attempt to mount such a study at a cost of US$100 million was terminated due to concerns of undue alcohol industry influence on the study design and lead researchers (Spiegelman et al., 2020). In the absence of RCT level evidence, we review evidence here from a) randomised experimental studies; b) genetic MR studies with short term outcomes known to be indicative of heart health, and c) higher quality observational studies with cohort or case-control designs. Mendelian randomisation (MR) is a method of studying the causal effects of modifiable exposures such as amount of alcohol use on health, social, and economic outcomes using genetic variants associated with the specific exposures of interest (here level of alcohol use) but not directly with the outcome of interest (i.e. a CVD-related disease). Observational studies are the most prone to the appearance of associations that are not causal. However, they are much easier to conduct and provide a larger volume of evidence than other study types, though there is significant variation in the quality of their methods as will be discussed.

Lifetime selection bias

The present review will pay particular attention to whether the SRMAs identified have assessed included studies for what Carr et al. (2024) describe as “reverse causation” and Naimi et al. (2017) refer to as “lifetime selection bias”. At the most basic level, this concerns the issue of whether non-drinkers, or abstainers identified as the comparison or reference group for people continuing to drink, suffer from contamination due to inclusion of former drinkers. Sometimes known as the "sick quitter effect", Roerecke and Rehm (2014) identify this as the most serious methodological problem with observational studies on alcohol and health. It is well established that current abstainers who previously drank alcohol tend to have poorer health and reduced life expectancy compared with lifetime abstainers. For example, Bergmann et al. (2013) demonstrated increased mortality risks for both former light to moderate and former heavy drinkers in a large multi-site prospective study.

To mitigate this problem, an increasing number of studies have attempted to separate former drinkers from the abstainer reference group. However, different research groups have addressed this problem with different degrees of rigour. Carr et al. (2024) estimated that 88 out of 95 cohort studies on alcohol and heart disease had dealt with "reverse causation" e.g. by removing former drinkers from the reference group. By comparison, Zhao et al. (2017) assessed that only 5/45 such studies had adequately addressed the problem. We outline the different criteria below.

A) *A limited definition of selection bias*: any study (e.g. Carr et al., 2024; Roerecke and Rehm, 2014) which takes steps to remove ex-drinkers or former drinkers from a miscellaneous group of abstainers (which may include some occasional or light drinkers).
B) *A strict definition of selection bias*: any study (e.g. Fillmore et al., 2006; Stockwell et al., 2016; Zhao et al., 2017) which strictly defines lifetime abstainers as excluding even former light or occasional drinkers. Henceforth we refer to whether studies have dealt with former and/or occasional drinker bias, or, more generically, as “abstainer bias”.

Naimi et al. (2017) describe how abstainer biases accumulate across the life course, citing evidence that as people age they tend to stop or cut down their drinking in response to ill-health. As a result, if no mitigating steps are taken, a reference group of current abstainers will increasingly with advancing age include people who are less healthy for reasons often unrelated to their alcohol use. A further consideration is that it is insufficient to separate former or even occasional drinkers from lifetime abstainers as groups of people continuing to drink can also be considered to be biased towards good health. The further necessary steps have rarely been taken. In a rare exception, Liang and Chikritzhs (2013) showed how reassigning former drinkers to current drinkers eliminated the appearance of protective effects in relation to heart disease. Bergmann et al. (2013) also conducted a sensitivity test in which when former moderate drinkers were combined with current moderate drinkers apparent cardiac protection was greatly reduced.

One further implication of Naimi et al.’s (2017) theory of accumulating lifetime selection bias is that studies recruiting participants at younger ages should be less prone to this problem than studies recruiting older cohorts. This has been confirmed subsequently in meta-analyses of IHD by Zhao et al. (2017) and all-cause mortality by Stockwell et al. (2024).

In discussion of the results and conclusions of SRMAs identified in this review, we will consider the extent to which lifetime selection bias has been addressed (partially or fully) or at least mitigated (e.g. by the use of relatively young cohorts followed up to older age).

The problem of underreporting of alcohol use in observational studies

It is well-established that self-report surveys of drinking levels and patterns in the general population substantially under report known alcohol sales, often covering only 40% of recorded consumption (Zhao et al., 2015). For various reasons, it appears that higher coverage rates (around 65%) are obtained from general population samples volunteering for epidemiological studies on health risk factors (Stockwell et al., 2018). These latter kinds of studies are the basis upon which morbidity and mortality risks are based in observational studies. However, underreporting as well as the prospect for differential underreporting for different subgroups, remains a problem for interpretation. There is evidence both for greater underreporting by heavier drinkers as well as by lighter, more occasional drinkers (Zhao et al, 2015). In general, however, this means that health risks may be slightly over-estimated. Objective measures of recent alcohol consumption have been developed some of which (e.g.Peth) are capable of detecting alcohol consumption over the past three or four weeks (Perelli et al, 2023). However, there has been no systematic uptake of this methodology to corroborate self-reported consumption and so this remains another key limitation of observational studies.

Alcohol industry funding and conflicts of interest

There is increasing awareness and concern regarding the influence of commercial vested interest groups on research conduct and interpretation, a concern that is particularly apparent in relation to the activities of alcohol industry bodies (e.g. Golder & McCambridge, 2024). While our main focus is on stated research designs and findings in this review, we will also note wherever potential conflicts of interest have been acknowledged by at least one co-author of a SRMA discussed. It cannot be assumed, however, that every co-author of a study has fully declared potential conflicts of interest created by receiving funding, fees or travel expenses from an alcohol industry related body.

Literature search methods

Relevant SRMAs were identified through searches of the scholarly databases (PubMed, Cochrane Library, Epistemonikos, International HTA, JBI, PsycNet, Web of Science)

conducted using the search term ‘‘alcohol*[Title]”, adapted to each specific type of cardiovascular disease and alternative terms as shown below. The searches conducted in the databases were restricted to SRMAs published between 2014 and 2024, inclusive (n=26). We will tabulate the main characteristics of the selected SRMAs by outcome type, listing main conclusions of study authors plus notes on the extent to which reverse causation (i.e. biases caused by "sick quitters" or people cutting down for health reasons) were dealt with by each SRMA.

CVD outcomes and alternative search terms:

- Ischaemic heart disease [or: ischemic heart disease, coronary heart disease, coronary artery disease, myocardial infarction, heart attack, acute coronary syndrome]
- Stroke, undifferentiated [or: cerebrovascular accident]
- Ischaemic stroke [or: ischemic stroke]
- Haemorrhagic stroke [or: hemorrhagic stroke, intracerebral hemorrhage, intracerebral haemorrhage]
- Atrial fibrillation [or: auricular fibrillation]
- Atrial flutter
- Heart failure [or: cardiomyopathy, alcoholic cardiomyopathy, congestive heart failure, cardiac failure]
- Peripheral artery disease [or: Peripheral vascular disease, PAD, PVD]
- Cardiovascular disease, undfferentiated
- Hypertension [high blood pressure]
- Type 2 diabetes [Adult-onset diabetes, diabetes mellitus type 2, or DM2]

Some of the included SRMAs presented estimates in categories of grams of ethanol consumed per day e.g. 1-20 g per person per day. Other SRMAs reported results in categories of numbers of "drinks" or "standard drinks" consumed per day. While definitions of these varied, most defined one drink as either 10 g or 12 g. In this review we will refer to "drinks" more generically to indicate a unit of ethanol consumed of approximately 10-12 g. Different levels of consumption were defined differently across studies. We will use generic terms such as low (up to one drink per day), moderate (one or two drinks per day) and heavy (more than two drinks per day) drinking volumes. This broadly reflects the levels used across this large literature.

In relation to alcohol and all-cause mortality (the outcome associated with the J-shaped curve) we identified a recent umbrella review (Sarich et al., 2024) which identified and assessed 25 previously published SRMAs.

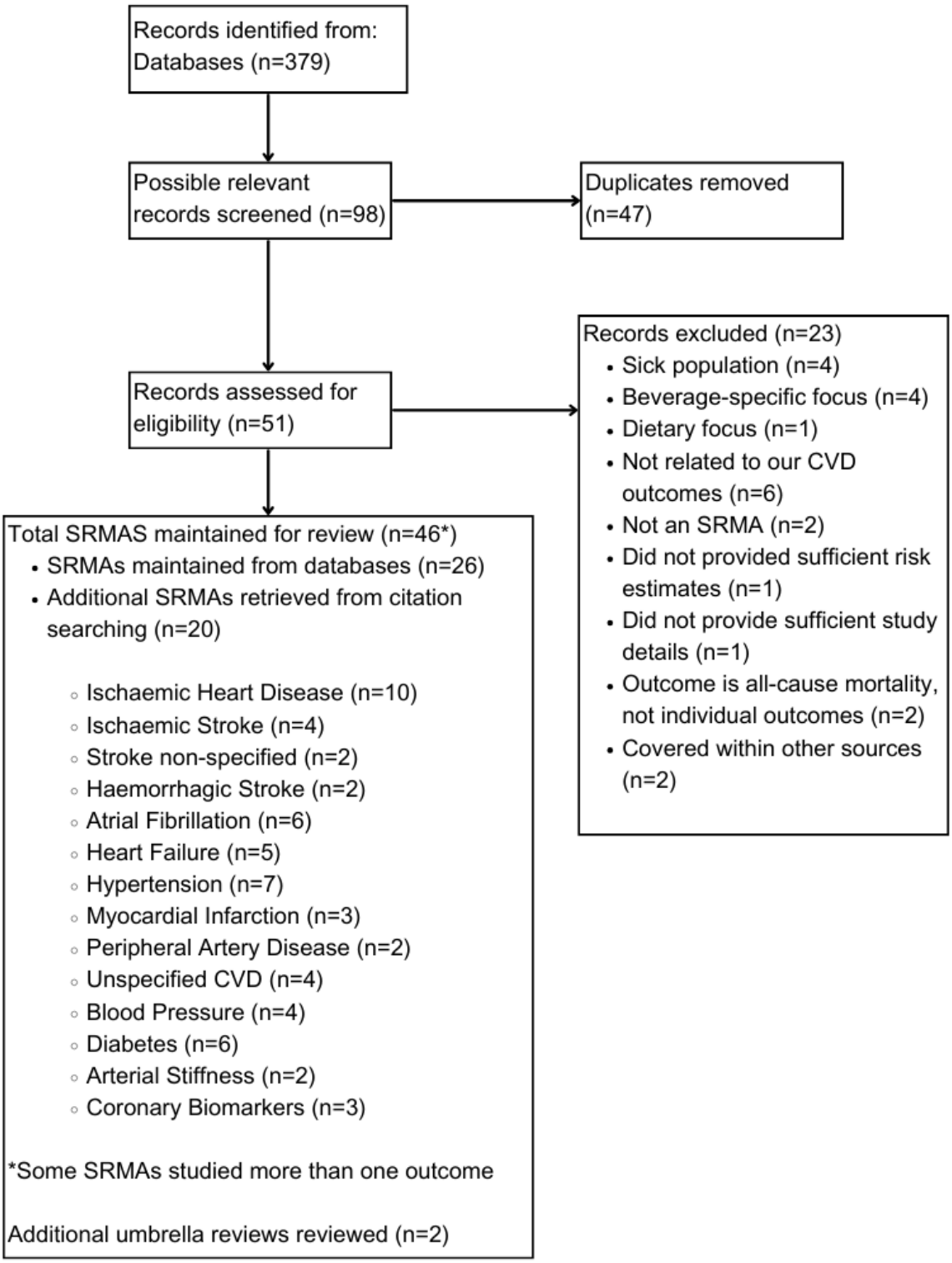
We also searched for conflict-of-interest statements in the identified SRMAs in this review for acknowledgement of alcohol industry funding or other associations so these could be noted alongside reported findings.

RESULTS

A PRISMA flowchart identifying numbers of reviews identified in relation to each disease category is provided in Figure 1. Inclusion criteria were SRMAs studying a healthy human population with a focus on one or more of our cardiovascular-related outcomes. After searching multiple scholarly databases, checking reference lists, and removing duplicates 71 studies were further examined for review, 23 studies were excluded for various reasons such as not including risk estimates for relevant outcomes for at least three levels of exposure to alcohol or for having a focus on different beverage types rather than total ethanol consumption. We identified an eligible 46 SRMAs and two umbrella reviews for this review. Identified reviews assessed IHD or MI (n=13), stroke (n=8), heart failure (n=5) atrial fibrillation (n=6), hypertension (n=7), peripheral artery disease (n=2), CVD in general (n=4), blood pressure (n=4), diabetes (n=6), arterial stiffness (n=2), and coronary biomarker (n=3) outcomes. We will summarise, discuss and critique the results of these SRMAs separately for each type of CVD outcome. One of the umbrella reviews (Sarich et al., 2024) concerned all-cause mortality and the other included a variety of CVD outcomes (Zhong et al., 2022) the results of which have been presented separately in the results by outcome type.

Of the 48 studies included in this umbrella review, 42 declared funding from non-industry sources (e.g., university research grants, research councils/centres, mental health services centres, medical institutes etc); 10 of these studies included an author who had received industry payments in the past (but not for the applicable studies). 2 (4.17%) studies declared funding from industry sources (Schrieks et al., 2015: “I.C.S. and H.F.J.H. were supported by…the Dutch Foundation for Alcohol Research, representing Dutch producers of and traders in beer, wine, and spirits”; Wilkens et al., 2022: “a PhD scholarship sponsored in part by a Carlsberg Foundation… Salaries for T.L.W., J.N.E., and L.O.D. were partly supported by grants from the Carlsberg Foundation”. Four studies did not declare funding sources.

Fig. 1 PRISMA flow chart demonstrating the systematic search process



Ischaemic heart disease (IHD)

No SRMAs of RCT studies were identified examining the association between alcohol use and risk of future IHD in general, or specifically myocardial infarction (MI).

Genetic studies

Carr et al. (2024) identified four MR studies in their comprehensive SRMA of alcohol and IHD, three of which used Asian populations (Chinese or Korean) and one a British population. They searched for all studies published between 1970 and 2021.

In each case likely levels of alcohol consumption were predicted from genetic profiles of participants. It was also necessary to demonstrate that the genetic profiles utilised had no independent relationship with the outcome of interest i.e. IHD. For example, no significant association would be found between IHD risk and these particular genetic profiles for people abstaining from alcohol.

The authors concluded that there was no significant association between alcohol use and IHD, whether positive or negative, when pooling results from the four identified studies and using a non-linear model to detect J-shape relationships. Given the recent and continuing evolving advancements in the field of MR, they also concluded that future studies employing a range of new, sophisticated MR methodologies were needed to increase confidence in this conclusion.

Van de Luitgaarden et al. (2021) identified 6 relevant studies on IHD using MR approaches and came to the same conclusion as Carr et al. (2024) i.e. there were mostly no significant relationships but improvements in methodology and future studies using more advanced MR methodologies were recommended. One of the studies reviewed produced results specifically for myocardial infarction (MI), a subset of IHD (Millwood et al., 2019) which reported no relationship between level of alcohol consumption and risk of MI. This was rated as a high quality study in the SRMA e.g. it included tests for non-linear risk relationships.

Table 1: Main conclusions from SRMAs of genetic studies on alcohol use and IHD incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Carr et al, 2024 Incidence & mortality	4 Mendelian Randomization studies	No significant associations reported in well-designed studies using a non-linear model. Need more higher quality studies to increase certainty.	None
Van de Luitgaarden et al., 2021 Incidence & mortality	6 Mendelian Randomization studies	No significant overall association reported in most studies. One study showed reduced IHD risk for low level consumption. Two assessed potential non-linearity and neither found clear evidence for protective effect of low-to-moderate drinking. Need more high-quality studies.	None

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

We identified 9 SRMAs assessing cohort and/or case-control studies relating level of alcohol use and risk of subsequent IHD incidence and/or mortality compared with abstainers (see Table 2). Two more assessed risk of MI specifically, a major sub-set of IHD (see Table 3). These SRMAs arrived at different conclusions depending on largely on how the issue of reverse causation or abstainer bias (i.e. sick-quitter type effects) was handled in study selection.

Carr et al. (2024) identified 95 cohort and 27 case-control studies on this topic of which they considered 88/95 and 25/27 respectively to have dealt with reverse causation appropriately. They adjusted study models for this variable which would likely bias estimates towards the small number of studies that did not adjust for reverse causation. They estimated significant protection against IHD for men but not women, both for morbidity and mortality outcomes. Maximum benefits were observed for men at approximately 20 g of ethanol per day. Relative risk estimates for women for low-volume consumption tended to be below 1.0 (i.e. indicating protection) but confidence intervals were wide and effects were not significant. The authors noted inconsistency in these results with the results of genetic studies discussed above. They list a number of reasons why observational studies like these may not provide accurate estimates, including residual and unmeasured confounding which is hard to eliminate.

Zhao et al. (2017) identified 45 cohort studies looking at alcohol use and IHD mortality outcomes. They reported evidence of protective effects from low-volume alcohol use in pooled analyses including all studies even after adjusting for a range of study design characteristics including a strict definition of reverse causation due to abstainer biases.

However, when an additional precaution was taken against selection bias, a nonsignificant protective effect was observed at up to approximately two drinks per day (RR=0.95, 95% CIs: 0.75, 1.21). This precaution involved selecting studies using younger cohorts recruited at an average of less than 56 years of age while still being followed up to higher ages at which IHD could be experienced. In contrast to Carr et al. (2024), only 7 out of the 45 studies were coded as having dealt with reverse causation (i.e. former or occasional drinker bias in the abstainer reference group).

O'Neill et al. (2018) conducted a meta-analysis of six prospective studies which included multiple measurement points over time. Their analysis focused on whether drinking status was consistent or varied over a 10 year period. They found that people drinking low-volume amounts consistently over time had significantly reduced risks of heart disease incidence. They also found that consistent heavy drinkers did not have an increased risk of heart disease. The authors interpret these findings as evidence for protective effects of low volume of alcohol use and recommend consistent adherence to low-risk drinking guidelines i.e. consistent low-volume drinking to improve health. However, their methods did not deal with selection biases created by people quitting or cutting down their drinking prior to the 10 year observation period. Furthermore, reverse causation is a plausible explanation of their findings i.e. healthy people self-selecting to be consistent in their drinking patterns.

Yang et al. (2016) estimated protective effects of alcohol use against IHD incidence for consumption up to 90 g of ethanol per day. They took no account of former and occasional drinkers in their currently abstaining reference group and so selection bias will have strongly affected these study estimates.

In a series of SRMAs by Roerecke and Rehm (2010, 2012 and 2014), evidence for IHD protection was observed for low volume alcohol intake even after adjustment for former drinker biases. However, this was only present among persons not reporting heavy episodic drinking i.e. consumption of at least 60 g of ethanol and one drinking occasion 12 or more times per year. These authors identified the "sick quitter" effect or failure to remove former drinkers from the abstainer reference group as the most significant methodological shortcoming in this literature. They estimated the impact of removing former drinkers and adjusted estimates for studies that fail to do this. Nonetheless, it is unclear how strictly they defined lifetime abstainers and they took no account of the effect of including occasional drinkers in the nondrinking reference groups. Many studies still include occasional drinkers in the reference group of so-called abstainers which Fillmore et al. (2006) and Stockwell et al. (2016) note will increasingly include people who have cut down on their drinking for health reasons.

Table 2: Main conclusions from SRMAs of observational studies on alcohol use and IHD incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Carr et al., 2024 Incidence & mortality	95 cohort 27 case-control	Cohort and case-control data show low to moderate alcohol consumption is associated with decreased IHD risk.	Only 9/122 (7.4%) studies assessed as having former drinker bias. A loose criterion applied.
O'Neill et al., 2018 Incidence & mortality	6 cohort studies	Instability in drinking behaviours over time is associated with risk of CHD. Abstainers and inconsistently moderate drinkers have increased CHD risk.	Strong selection bias present. Reverse causation a plausible explanation of results.
Zhao et al., 2017 Mortality	45 cohort studies	An association between alcohol use and reduced IHD risk was observed in pooled analyses but not studies of those aged 55 years or younger at baseline or higher quality studies.	38/45 (84.4%) studies assessed as having abstainer bias. Mitigated by using younger cohorts and statistical adjustment.
Yang et al., 2016 Incidence	18 prospective studies	Alcohol consumption in moderation is associated with a reduced risk of CAD with 36 grams/d of alcohol conferring a lower risk than other levels. Protection estimated up to 90g ethanol per day.	Strong selection bias present. No account of abstainer group biases made.
Zheng et al., 2015 Incidence & mortality	9 cohort studies 2 nested case-control studies	Low-to-heavy alcohol intake might be protective against coronary disease risk in men and women.	Substantial bias.
Roerecke Rehm, 2014 Incidence & mortality	N studies not stated	Evidence for a beneficial effect of low alcohol consumption without heavy drinking episodes is strong, corroborated by experimental evidence. However, episodic and chronic heavy drinking do not provide any beneficial effect on IHD.	Partial adjustment for abstainer biases applied. Only former not occasional drinker bias considered.
Roerecke Rehm, 2012 Incidence & mortality	44 cohort and case-control studies	A cardioprotective association between alcohol use and IHD cannot be assumed for all drinkers, even at low levels of intake.	Former drinker bias partly dealt with, occasional drinker bias not.
Ronksley et al., 2011 Incidence & mortality	60 cohort studies	Relative to non-drinkers, low and moderate level drinkers had reduced risk of IHD incidence and mortality. The lowest risk of IHD mortality occurred with 1–2 drinks a day.	Substantial, all non-drinkers used as reference group.
Roerecke Rehm, 2010 Incidence & mortality	14 cohort studies	The cardioprotective effect disappears when light to moderate drinking is mixed with irregular heavy drinking occasions.	Substantial.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Both SRMAs evaluating observational studies of alcohol consumption and risk of MI, concluded there was evidence of protective effects from alcohol use. Liu et al. (2017) identified 18 cohort studies relating level of alcohol use to MI risk. Perhaps uniquely among all the outcomes examined in this report, it was concluded there was a linear, negative association with a significant dose response effect i.e. higher levels of drinking were increasingly associated with lower levels of MI risk. While there was substantial selection bias potentially introduced in this SRMA by the use of nondrinkers without exclusion of former drinkers as the reference group, a number of studies also used light or low-level drinking as the reference group which should be less prone to selection bias.

Mostofsky et al. (2017) identified five case-control and four cohort studies exploring the relationship between recent alcohol use and risk of MI. In meta-analysis, they estimated a U-shaped association between alcohol intake and MI risk, with modest benefits at approximately 2 drinks drunk in the past 24 hours and increasing risk thereafter. A lower risk of MI was also estimated for moderate alcohol use from studies looking at drinking level over the week before an MI event and a higher risk for heavy alcohol consumption i.e. a J-shape risk association. No effort was made to assess impact of former drinking on MI risk though arguably this kind of bias may be less significant for an assessment of acute outcomes over days and weeks.

Table 3: Main conclusions from SRMAs of observational studies on alcohol use and myocardial infarction incidence and/or mortality risk and likely extent of selection bias

Study	N studies	Main Conclusions	Selection bias*
Liu et al., 2017 Incidence & mortality	18 cohort studies	Increasing drinking levels were significantly associated with reduced risk of MI onset i.e. a negative correlation between drinking and MI risk.	Yes, "non-drinkers" used as reference.
Mostofsky et al., 2016 Incidence & mortality	5 case-crossover studies 4 case-control studies	A U-shaped association between alcohol intake in past 24 hours and MI risk. Also lower risk of MI with moderate alcohol intake in past week.	Some bias possible but focus on acute effects.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Conclusions on IHD

Genetic studies find no evidence of beneficial or protective effects of low-dose alcohol against IHD or MI (Carr et al., 2024) even after testing for non-linear models. SRMAs of

observational studies (cohort and case-control) find varying evidence for protective effects of low-dose alcohol depending on steps taken to mitigate reverse causation (i.e. abstainer biases). The SRMA taking the most complete steps to reduce these biases (Zhao et al., 2017) found small but not statistically significant protective effects after excluding studies at high risk of bias. This SRMA was identified in the recent Canadian Guidance and Alcohol Health as being of highest quality (Levesque et al., 2024). The SRMAs focusing specifically on MI outcomes (Table 3) found evidence for acute benefits of recent alcohol consumption (last 24 hours, past week) plus a unique, linear negative association between level of drinking and MI risk. While the problem of abstainer bias was not addressed in these studies, it is not possible to discount these findings given this unique pattern of results. However, it should be noted that the nine other SRMAs dealing with IHD in general will all have included MI outcomes which are a substantial proportion of IHD cases overall i.e. these findings should not be interpreted in isolation from those on IHD outcomes in general.

Stroke (unspecified type)

Genetic Studies

Van de Luitgaarden et al. (2021) included four MR studies in their SRMA examining either ischaemic or haemorrhagic stroke outcomes for alcohol consumers. None of the included studies found evidence for protective effects, one of which tested for non-linear (i.e. J-shaped) relationships. Two studies found evidence for an overall positive association between alcohol use and stroke risk. They recommended that additional analyses in future studies should test for non-linear effects.

Table 4: Main conclusions from SRMAs of genetic studies on alcohol use and ischaemic and/or haemorrhagic stroke incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Van de Luitgaarden et al., 2021 Incidence & mortality	4 Mendelian Randomization studies on ischaemic and/or haemorrhagic stroke	No significant protective associations at any consumption level. One study tested non-linear models. Positive overall association reported.	None

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

Two SRMAs provided results for all types of stroke without specification of subtypes (Ronksley et al., 2011; Zheng et al., 2015). Neither of these analyses took account of potential selection biases as they employed all kinds of non-drinkers as a reference group. Zheng et al. (2015) also included occasional or light drinkers combined with non-drinkers as the reference. Analysing seven cohort studies, Zheng et al. (2015) found evidence for protective effects from alcohol for moderate drinking women but not men. Ronksley et al. (2011) included 27 prospective studies and found nonsignificant association between moderate drinking men and women and risk.

Table 5: Main conclusions from SRMAs of observational studies on alcohol use and stroke (non-specified) incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Zheng et al., 2015 Incidence & mortality	7 cohort studies	There was reduced stroke risk for moderate drinking women but not men.	Substantial, non-drinkers in reference group.
Ronksley et al., 2011 Incidence & mortality	27 prospective cohort studies	Relative to non-drinkers, low and moderate level drinkers had reduced risk of stroke incidence and mortality. The lowest risk of stroke mortality occurred with 1–2 drinks a day.	Substantial, non-drinkers as reference group.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Conclusions for unspecified strokes

SRMAs of genetic studies find no evidence of protective effects overall for unspecified types of stroke though non-linear analysis to specifically test for J-shaped risk relationships were only conducted in one of the reviewed studies. The two available SRMAs of observational both ignored the issue of potential selection bias and hence will have underestimated both incidence and mortality risks for moderate alcohol consumers. Nonetheless, the SRMA canvassing the most studies (Ronksley et al., 2011) found no significant association between moderate alcohol consumption and stroke risk for either men or women. Again, this may be an underestimate of actual risk due to the effects of systematic bias on the abstainer reference groups.

Ischaemic Stroke

Observational studies

Larsson et al. (2016) identified 25 cohort or case-control studies focusing on the relationship between usual alcohol consumption and risk of ischaemic stroke. They concluded that low to moderate alcohol consumption (up to two drinks per day) was associated with significantly reduced risk of ischaemic stroke while higher levels increased risk. Their reference group included current abstainers, lifetime abstainers and occasional drinkers i.e. their main analyses suffered from both former and occasional drinker biases. A sensitivity analysis was reported as finding mostly no difference depending on the type of reference group used. However, a strict definition of lifetime abstainer was not specified. Furthermore, when occasional drinkers were the reference group in studies, no protective effects of low-volume alcohol use were detected.

Mostofsky et al. (2016) identified nine case-control and case-crossover studies focusing on the relationship between recent alcohol consumption and the acute risk of a cardiovascular event. They concluded that within the first 24-hours following even low or moderate consumption, there was an increased risk of cardiovascular events including ischaemic stroke. Up to one week later they found evidence of protective effects for ischaemic stroke for low-dose alcohol but only detrimental effects for higher dosages.

Table 6: Main conclusions from SRMAs of observational studies on alcohol use and ischaemic stroke incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Larsson et al., 2016 Incidence and/or mortality	25 prospective studies	Light and moderate alcohol consumption was inversely associated with ischemic stroke, whereas heavy drinking was associated with increased risk.	Substantial. But no benefits if occasional reference group.
Mostofsky et al., 2016 Incidence & mortality	9 case-control or case-crossover studies	There appears to be a consistent finding of an immediately higher cardiovascular risk following any alcohol consumption, but, by 24 hours, only heavy alcohol intake conferred continued risk.	Some bias likely.
Zheng et al., 2015 Incidence & mortality	5 cohort studies	There was reduced ischaemic stroke risk for low level drinking women and men plus moderate drinking women.	Substantial, non-drinkers in reference group.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

No attempt was made to assess lifetime drinking patterns in either type of study design. In case-control studies, therefore, currently abstaining controls may have been former drinkers or misclassified occasional drinkers. Thus, it is likely some selection bias affects the analyses in this review.

Conclusions for ischaemic stroke

Three SRMAs of observational studies were identified for this outcome, none published after 2016. Some evidence of protective effects was identified in two SRMAs for low-volume alcohol use though Mostofsky et al. (2016) found increased risks up to 24-hours after consumption. None of these reviews took full account of the potential for reverse causation as a result of including former and/or occasional drinkers in the reference group. We conclude that more a critical and updated analysis is required to determine whether low-dose alcohol can have protective effects against ischaemic stroke. Both reviews consistently confirmed increased risks from higher levels of alcohol consumption. Risk estimates here may be underestimated because of selection biases.

Haemorrhagic stroke

Observational studies

Two of the same SRMAs as for ischaemic stroke were the only ones identified in our literature search for haemorrhagic stroke. As discussed above, both suffer from a degree of selection bias which could lead to either exaggerating protection or underestimating the risk from low to moderate consumption.

Thus, while Larsson et al. (2016) estimated no association either way between low to moderate alcohol consumption (up to two drinks per day), had selection bias been accounted for, an increased risk of haemorrhagic stroke might have emerged even at moderate consumption levels. Significantly increased risks were detected above four drinks per day.

Mostofsky et al. (2016) found evidence for increased risk of haemorrhagic stroke within 24 hours of consuming any level of alcohol in comparison with abstinence. They also estimated significantly reduced risk up to one week thereafter for low volume use. However, it is unclear the extent to which selection bias may have impacted this estimate.

Table 7: Main conclusions from SRMAs of observational studies on alcohol use and haemorrhagic stroke incidence and/or mortality risk and steps to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Larsson et al., 2016 Incidence & mortality	11 prospective studies	Light and moderate alcohol consumption was not associated haemorrhagic stroke, whereas heavy drinking was associated with increased risk.	Substantial bias.
Mostofsky et al., 2016 Incidence & mortality	7 case-control or case-crossover studies	Immediately higher cardiovascular risk following any alcohol consumption, but, by 24 hours, only heavy alcohol intake conferred continued risk.	Some bias likely for case-control studies.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Conclusions for haemorrhagic stroke

Low to moderate level alcohol use does not protect against haemorrhagic stroke while higher levels (e.g., four or more per day) are associated with increased risks. More attention to selection bias is needed in this literature as this may have led to an underestimation of the risk at all levels of consumption.

Atrial fibrillation (AF)

Experimental Studies

While no SRMA was identified in the systematic search examining experimental studies with AF outcomes, one high quality RCT was identified (Voskoboinik et al., 2020) in which individuals drinking more than 10 drinks a week and who had experienced AF were randomised into an intervention to reduce or control. A large majority (80%) of individuals reduced their drinking in the intervention group compared with 20% in the control. There was a significant reduction in AF recurrence in the abstinence intervention group at 6 months follow up. Average intake prior to intervention in this group was 16.8 drinks per week i.e. just above two drinks per day, a level often equated to "moderate drinking".

Genetic Studies

A review of two MR studies found no evidence of protective effects for atrial fibrillation (AF) or flutter though non-linear analyses were not conducted to specifically test for J-shaped risk relationships.

Table 8: Main conclusions from SRMAs of genetic studies on alcohol use and atrial fibrillation incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Van de Luitgaarden et al., 2021 Incidence & mortality	2 Mendelian Randomization studies	No significant overall association reported but only linear models tested. Need more high-quality studies to test non-linear risk relationships.	None.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

Five SRMAs were identified for this outcome, variously published between 2014 and 2023, estimating effects for between six and 13 mostly prospective observational studies. Conclusions made by authors across the studies were quite consistent, perhaps not surprisingly as there was much overlap in the original studies identified for meta-analysis. No protective effects were reported for AF and some evidence of increased risk at low levels of consumption were found for males (e.g. at one drink per day). Most found increased AF risk at moderate levels of consumption (approximately two drinks per day) and all reported increased risk for higher levels of consumption. None of the SRMAs made efforts to only include studies free from selection bias i.e. former and/or occasional drinkers were explicitly present in the reference groups used. This raises the possibility that AF risk was underestimated at every level of consumption.

Only one study (Larsson, Drca and Wolk, 2014) included atrial flutter as an outcome which was combined with atrial fibrillation. It is therefore not possible to make separate conclusions about these outcomes.

Table 9: Main conclusions from SRMAs of observational studies on alcohol use and atrial fibrillation incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Grindal et al., 2023 Incidence	2 retrospective and 7 cohort studies	Increased alcohol consumption is associated with an increased risk of AF recurrence after catheter ablation for AF. Reduction of alcohol consumption may be beneficial in this context.	Substantial potential bias.
Yang et al., 2022 Incidence	13 cohort studies	Males who drink at low or moderate levels are at risk of incident AF. No protective effects evident.	Substantial potential bias.
Gallagher et al., 2017 Incidence	9 prospective studies	Low levels of alcohol intake were not associated with the development of AF. Moderate alcohol intake increases AF risk in males but not females. High alcohol intake is associated with a heightened AF risk for both males and females.	Substantial potential bias.
Larsson, Drca and Wolk, 2014 Incidence	7 prospective studies	Findings indicate that alcohol consumption, even at moderate intakes, is a risk factor for atrial fibrillation.	Substantial potential bias.
Samokhvalov, Irving & Rehm, 2010 Incidence	6 cohort studies 1 case-control study	Epidemiological criteria for causality were met to conclude a causal impact of alcohol consumption on the onset of AF with a monotonic dose–response relationship.	Substantial, non-drinkers as the reference group.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Conclusions for atrial fibrillation (AF)

There was evidence of increased AF risk for low levels of consumption in males and for increased risk for both males and females at higher levels of consumption. No protective effects were detected. An RCT with a 6 month follow up found decreased risk of AF recurrence among people who reduced their drinking (Voskoboinik et al., 2020). It is possible that underestimation of AF risk was present at all levels of consumption in the observational studies as systematic downward bias was present due to both former and occasional drinkers being allowed in the reference group.

Heart failure

Genetic studies

A review including two MR studies found no evidence of protective effects for heart failure though non-linear analysis were not conducted to specifically test for J-shaped risk relationships.

Table 10: Main conclusions from SRMAs of genetic studies on alcohol use and heart failure incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Van de Luitgaarden et al., 2021 Incidence & mortality	2 Mendelian Randomisation studies	No significant overall association reported but only linear models tested. Need more high-quality studies to test non-linear risk relationships.	None.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

A total of four SRMAs and one umbrella review assessing alcohol as a risk factor for these outcomes were identified, none of which adequately considered the problem of lifetime selection bias.

Arafa et al. (2023) presented a meta-analysis of seven cohorts from multiple countries using “light or moderate” drinkers as the reference group. For some studies they reported estimates for "abstainers" but it is not clear how many of these had excluded former or occasional drinkers. At least one cohort study did remove former drinkers from the abstainer group, however. They concluded there was a J-shaped curve such with both abstainers and heavy drinkers having significantly higher risk of cardiomyopathy than light or moderate drinkers.

Ihekire et al. (2023) conducted an umbrella review identifying 13 previous narrative or other reviews. They only provide a high-level conclusion, namely that consuming more than 80 g of ethanol per day for at least five years is associated with increased risk of heart

failure/cardiomyopathy. It contains no discussion of the issue of systematic bias and likely the material covered overlaps with those of the other four SRMAs we have identified.

Rehm et al. (2017) present a systematic review but no meta-analysis on this topic as methods used were too heterogeneous. They discussed findings from a range of different study types, identifying 26 relevant studies. They did not discuss the potential for systematic biases due to former or occasional drinkers contaminating reference groups. Their main conclusion was that heavy consumption of approximately 80 g per day or more was significantly associated with increased HF risk. They do not suggest protective effects at lower doses.

Larsson, Wallin and Wolk (2018) reported a systematic review and meta-analysis of 13 cohort studies estimating the association between level of alcohol use and risk of heart failure. They reported a J-shaped risk relationship with reduced risk for light drinkers and no increased risk for heavier drinkers. Notably, this SRMA did examine differences between subgroups of studies with different kinds of reference group including one described as consisting of "lifetime abstainers". A J-shaped curve was observed even for these studies. The importance of the reference group issue was highlighted by their confirming increased HF risk for former drinkers. It is unclear if a strict or loose definition of lifetime abstention was applied or if occasional drinker bias was also considered. This SRMA, however, provides the strongest evidence of potential health benefits of light alcohol use in relation to HF.

Larsson, Orsini and Wolk (2015) reported a systematic review and meta-analysis of eight cohort studies estimating the association between level of alcohol use and risk of heart failure. They reported a J-shaped risk relationship with reduced risk for light to moderate drinkers and increased risk for heavier drinkers. The reference group is simply referred to as "nondrinkers" and there is no discussion of the need to exclude former drinkers let alone occasional drinkers.

Conclusions for heart failure

A consensus conclusion across the five SRMAs identified examining this outcome in observational studies is that heavy alcohol use over at least five years is associated with increased risk while there is some suggestion of protective effects of light to moderate volume drinking (i.e. up to approximately two drinks per day). The latter conclusion was evident in the only SRMA (Larsson, Wallin and Wolk , 2018) to consider and attempt to adjust estimates for selection biases affecting the reference group. However, even in this

study it is unclear if more than a partial adjustment was made. Furthermore, the genetic studies suggest no protective effects add light to moderate levels of consumption.

Table 11: Main conclusions from SRMAs of observational studies on alcohol use and heart failure incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias
Arafa et al., 2023 Incidence	6 prospective cohort studies	Results indicated a J-shaped association between alcohol consumption and HF risk among Japanese men.	Substantial, non-drinker reference.
Ihekire et al., 2023 Incidence & mortality	13 literature reviews	The findings of this systematic review indicated that the likelihood of ACM occurrence significantly rose when the consumption of over 80 g of alcohol per day occurred for at least five years.	Likely substantial.
Larsson, Wallin and Wolk, 2018 Incidence	13 prospective studies	Light alcohol drinking was associated with a lower risk of HF. Former drinking was associated with a higher risk of HF.	Substantial, non-drinker reference.
Rehm et al., 2017 Incidence and mortality	26 observational studies	There were clear indications that heavy drinking (≥80 g per day) over several years was linked to high risk of cardiomyopathy, with greater lifetime exposure of alcohol linked to higher risks.	Substantial bias.
Larsson, Orsini and Wolk, 2015 Incidence & mortality	8 prospective studies	A J-shaped relationship was estimated with moderate use associated with a reduced risk of HF, heavy use an increased risk compared with 'non-drinkers'.	Substantial bias.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Hypertension

Genetic studies

Chen et al. (2008) was the only SRMA we could identify that considered hypertension as an outcome and that evaluated genetic studies. They identified three Mendelian randomisation studies and concluded a dose response impact of alcohol use on hypertension risk with no

evidence of protective effects. More high-quality studies of this kind are likely needed employing a variety of genetic instruments as surrogates of global consumption level.

Table 12: Main conclusions from SRMAs of genetic studies on alcohol use and hypertension incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Chen et al., 2008 Incidence	3 Mendelian Randomisation studies	These findings support the hypothesis that alcohol intake has a marked linear effect on blood pressure and the risk of hypertension.	None.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

Six SRMAs were identified that evaluated prospective studies and level of alcohol consumption at baseline and subsequent risk of developing hypertension (see Table 12). Five of these concluded there were no protective effects at low to moderate daily consumption levels and, further, there was a linear relationship between alcohol use and risk of hypertension. The sixth SRMA estimated a J-shaped relationship for women but not men. Notably, only Taylor et al. (2009) estimated effects for ex-drinkers. The most recent SRMA had the most relevant studies (n=23, Cecchini et al., 2024) and estimated linear relationships, especially for men. Given the absence of adjustment for selection bias involving the abstainers/non-drinker reference group it is likely that the risk of hypertension from alcohol use has been underestimated in these studies.

Cecchini et al. (2024) reported a comprehensive SRMA incorporating results from 23 cohort studies. While there is a discussion of varied estimates across studies and methods of assessing drinking at different time points from just one baseline measure to a complete lifetime assessment, there is no examination of the influence of reference group choice or discussion of the topic of systematic bias. Nonetheless, a linear positive relationship was estimated for risk of hypertension as a function of level of alcohol consumption which was especially steep for men. For women significant risk occurred above one drink per day but no protective effect was estimated.

Jung et al. (2020) performed a sophisticated SRMA using estimates of hypertension risk from 11 studies, 10 of which were cohort and one a case-control design. They presented results for the whole sample as well as disaggregated estimates for Asian and Western populations. They describe their reference group as containing both lifetime abstainers and

occasional drinkers i.e. there is reference group bias potentially present. They estimated a linear increase in risks of hypertension with no safe level among male Asian populations but higher thresholds of consumption for Western populations though no evidence of protective effects was reported. It is likely that the identified studies did not permit a consistent use of lifetime abstainers as the reference group and hence estimates of risk may be on the low side.

Table 13: Main conclusions from systematic reviews of observational studies on alcohol use and hypertension incidence risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Cecchini et al., 2024 Incidence	23 cohort studies	Results lend support to a causal association between alcohol consumption and risk of hypertension, especially above an alcohol intake of 12 g/day.	Substantial bias.
Jung et al., 2020 Incidence	10 cohort studies + 1 case-control study	Even low doses of alcohol can lead to the development of hypertension, particularly in Asian men.	Substantial bias likely.
Liu et al., 2020 Incidence	31 Cohort studies	Linear increase in hypertension with consumption. No evidence of a protective effect of alcohol consumption among women.	Substantial bias.
Roerecke et al., 2018 Incidence	20 cohort and case-control studies	Any alcohol consumption was associated with an increase in the risk for hypertension in men. No evidence for a protective effect of alcohol consumption in women.	Substantial bias.
Briasoulis, Agarwal, & Messerli, 2012 Incidence	16 cohort studies	There is a trend toward increased risk of hypertension with low and moderate alcohol consumption. The relationship between alcohol consumption and hypertension is J-shaped in women.	Substantial bias.
Taylor et al., 2009 Incidence	12 cohort studies	The risk for hypertension increases linearly with alcohol consumption, so limiting alcohol intake should be advised for both men and women.	Adjustment for "ex-drinkers".

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Curiously, only the oldest study by Taylor et al. (2009) made some attempt to adjust for potential selection bias affecting the reference group of non-drinkers. Specifically, they excluded "ex-drinkers" from the reference group but it is still likely that a less strict definition of lifetime abstaining was supplied including contamination by occasional drinkers.

Nonetheless, this SRMA concluded a significant dose response i.e. linear effect of alcohol use on risk of hypertension with no safe threshold.

Because hypertension is a risk factor for IHD, the question arises as to why no protective effects were found for low-dose alcohol and hypertension despite there being no adjustment for lifetime selection biases assessed in these SRMAs. One plausible explanation is that hypertension incidence typically occurs at a younger age than IHD mortality so these biases will be less developed. There could also be some empirical difference between the profiles of people at risk of hypertension and different mechanisms of alcohol's effect in play. A much broader array of people will receive a diagnosis of hypertension than will die from IHD and hence coronary risk factors may be less important. We will review the evidence below for effects of low-dose alcohol and blood pressure, clearly a specific biological pathway leading to potential hypertension which may be easier to detect in observational studies than the link between alcohol use and IHD mortality.

Conclusion for hypertension

Even low-volume alcohol consumption is a risk factor for hypertension for both men and women. The level of this risk may be underestimated by the failure in the relevant studies to account for systematic bias in the abstainer/non-drinker reference group.

Peripheral artery disease (PAD)

Genetic studies

Table 14: Main conclusions from SRMAs of genetic studies on alcohol use and peripheral artery disease incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Van de Luitgaarden et al., 2021 Incidence & mortality	1 Mendelian Randomization study	A significant linearly increasing risk of PAD was found for each additional drink consumed per week, but no tests for non-linear risk relationships.	None.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al, 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

One MR study was identified by Van de Luitgaarden et al. (2021) that assessed the risk relationship between level of alcohol use and PAD risk (Larsson et al, 2020). This study estimated significantly increased risk for each additional drink of alcohol per week but did not test for non-linear (e.g. you or J-shaped) risk relationships.

Observational studies

A SRMA of nine observational studies by Yuan et al. (2024) and estimated a U-shaped risk relationship when using a miscellaneous group of "nondrinkers" (including former drinkers) as the reference. Their conclusion, therefore, of protective effects for light and moderate drinking is therefore questionable as no effort was made to exclude selection bias. However, it is noticeable that the nadir of the U-shaped curve was at just two drinks per week. Other researchers (e.g. Ortola et al., 2024) have argued that such low-level drinking is a superior, less biased reference group and arguably the risks for all other levels of consumption should have been compared with this.

Table 15: Main conclusions from SRMAs of observational studies on alcohol use and Peripheral Artery Disease incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Yuan et al., 2024 Incidence & mortality	4 cohort studies 3 cross-sectional 2 case-control	Alcohol intake ≤2 drinks/week was associated with a reduced risk of PAD, while risk increased at ≥10 drinks/week.	Yes, included former drinkers in reference group

* This refers only to our assessment of whether lifetime selection bias (Naimi et al, 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Conclusions for PAD

While more well-designed studies are needed to assess the risk relationship between level of alcohol use and PAD, the identified SRMAs finding, respectively, one MR study and nine observational studies can be interpreted as evidence against moderate alcohol use having protective effects. We suggest that the SRMA of observational chose the wrong reference group and had they used two drinks per week as the reference there would have been no appearance of protective effects. Arguably at two drinks per week there are no physiological benefits - or if there are it is important to note that such benefits would be optimal at this very low level.

Cardiovascular disease (CVD) unspecified

Studies included here used outcomes with several CVD subtypes combined. Mostly they included IHD and at least one kind of stroke plus miscellaneous other CVD subtypes.

Genetic studies

A review finding three MR studies found no evidence of protective effects for unspecified CVD though no non-linear analysis has been conducted to specifically test for J-shaped risk relationships.

Table 16: Main conclusions from SRMA of genetic studies on alcohol use and unspecified CVD incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Van de Luitgaarden et al., 2021 Incidence/mortality	3 Mendelian Randomization studies	No significant overall association reported but only linear models tested. Need more high-quality studies to test non-linear risk relationships.	None.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

Three SRMAs reporting generalised results for CVD incidence or mortality were identified. They all concluded that light and/or moderate drinking was associated with reduced CVD risk. Unfortunately, none of the reviews took account of systematic biases hence all risk estimates are likely underestimated and benefits cannot be confirmed.

Conclusion for CVD in general

The health benefits observed in observational studies cannot be confirmed due to a failure to address the problem of selection biases likely affecting the nondrinking reference groups used. Thus, confounding and misclassification of drinking status remain concerns. Genetic studies find no evidence of protective effects of light to moderate drinking but further studies and analyses are required to confirm there is no underlying J-shaped relationship.

Table 17: Main conclusions from SRMAs of observational studies on alcohol use and unspecified CVD incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Yoon et al., 2020 Incidence	7 prospective cohort studies	Protective effects of light to moderate and moderate consumption for those aged between 41 and 65.	Substantial, non-drinkers the reference group.
Park et al., 2015 Mortality	2 cohort and 1 case-control study	All studies reported a non-significant effect of occasional or mild alcohol consumption.	Substantial, non-drinkers the reference group.
Ronksley et al., 2011 Mortality	21 prospective cohort studies	Relative to non-drinkers, low and moderate level drinkers had reduced risk of CVD and mortality. The lowest risk occurred with 1–2 drinks a day.	Substantial, non-drinkers as reference group.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

All-cause mortality

We identified a recent umbrella review which summarised results from 25 SRMAs on alcohol and death from all causes (Sarich et al., 2024), an outcome classically associated with the J-shape curve, and assessed the likely degree of bias including from inclusion of former drinkers among abstainer reference groups. They identified five of the 25 SRMAs as having addressed former drinker bias to some degree, three of which estimated some degree of reduced mortality risk from low to moderate drinking and two did not. Only one of these five SRMAs was assessed as being at low risk of bias overall (Stockwell et al., 2016) and this one estimated no significant benefits for consumption up to 24 g of ethanol or approximately two drinks per day. Two more recent SRMAs confirm this latter conclusion (Zhao et al., 2023; Stockwell et al., 2024).

CVD risk factors: 1. Blood pressure levels

Short term experimental studies

Two SRMAs were identified for the intermediate outcome of raised blood pressure that used short-term RCTs in which subjects were randomly assigned to receive low doses of alcohol or no alcohol (Tasnim et al., 2020; Roerecke et al., 2017). Thus, the systematic biases that plague observational studies are dealt with by the randomisation of alcohol exposure versus none.

In a Cochrane review, Tasnim et al. (2020) identified 32 randomised controlled trials regarding the short-term effects of alcohol on heart rate and blood pressure, distinguishing between the first six hours, 7 to 12 hours and more than 12 hours after consumption. A biphasic effect was observed for blood pressure for doses of alcohol greater than 24 g (i.e. above about two drinks) whereby there was initially a reduction followed by a significant increase 13 or more hours later. Blood pressure was mostly unaffected at lower doses initially. Heart rate increased significantly in the short and longer term at all dosage levels.

Longer term experimental studies

Roerecke et al. (2017) identified 36 experimental studies involving trials reducing alcohol consumption on blood pressure over periods of one week to two years. The latter included a two-year long RCT of diabetic individuals randomly assigned to receive one drink with a meal each day of either wine or water i.e. a strong research design (Gepner et al, 2016). Experimental trials of interventions to reduce alcohol consumption among those drinking two or more drinks at baseline resulted in reduced blood pressure.

Table 18: Main conclusions from SRMAs of experimental studies on alcohol use and blood pressure and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Tasnim et al., 2020	32 RCTs	High-dose alcohol has a biphasic effect on BP; it decreases BP up to 12 hours after consumption and increases BP > 13 hours after consumption. High-dose alcohol increases HR at all times up to 24 hours.	No bias.
Roerecke et al., 2017 Incidence	15 parallel-arm & 21 crossover trials	A reduction in alcohol consumption resulted in a decrease of blood pressure in those drinking two or more drinks per day at baseline.	No bias.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Genetic studies

A relatively early SRMA by Chen et al. (2008) identified five MR studies addressing the association between alcohol use, blood pressure and risk of hypertension. They concluded a strong positive association though it is not clear if non-linear relationships were directly tested.

Table 19: Main conclusions from SRMAs of genetic studies on alcohol use, blood pressure and hypertension

Study	N studies	Main Conclusions	Selection bias*
Chen et al., 2008 Blood pressure	5 mendelian randomisation studies	These findings support the hypothesis that alcohol intake has a marked effect on blood pressure and the risk of hypertension.	None.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

Di Federico et al. (2023) identified seven observational studies examining the relationship between self-reported alcohol use and blood pressure with an average of five years follow-up. Results suggested the association between alcohol consumption and blood pressure was direct and linear with no evidence of a threshold for the association. This SRMA did not appear to take account of systematic biases affecting the nondrinking reference group so it is possible that the estimated impacts of alcohol on blood pressure presented are underestimated.

Table 20: Main conclusions from SRMAs of observational studies on alcohol use and blood pressure and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Di Federico et al., 2023 Incidence & mortality	7 cohort studies	Results suggest the association between alcohol consumption and systolic blood pressure is direct and linear with no evidence of a threshold for the association.	Present, non-drinkers the reference.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Conclusions for blood pressure

Observational studies indicate linear, dose response effects of alcohol on blood pressure, a pattern confirmed in longer term experimental studies. One high quality review (Tasnim et al., 2020) of experimental studies identified short term reductions in blood pressure after low-dose alcohol administration but this was followed by increases in the longer term. Longer term impacts estimated for low to moderate level drinkers in the SRMA of observational studies were also likely underestimated by not taking account of selection biases in the nondrinking abstainer group.

CVD risk factors: 2. Blood glucose control in diabetics and non-diabetics

Experimental studies

Schrieks et al. (2015) performed a SRMA of 14 intervention studies looking at impacts on biomarkers related to blood glucose among those without diabetes with outcomes assessed at up to two weeks for alcohol randomised administration versus none or placebo. Their main finding was that no association was found with insulin sensitivity, contrary to findings from some observational studies. There was some evidence, however, of benefits from alcohol in relation to fasting insulin and haemoglobin A1c levels (curiously an indicator of much longer-term blood sugar levels). However, it is unclear how relevant such short-term effects for risk of type II diabetes especially when assessed in non-diabetic populations. Furthermore, the authors declared receipt of alcohol industry funding. By contrast, in a two-year RCT involving daily low dose alcohol administration with a meal versus water in a diabetic population, Gepner et al. (2015) found no evidence for significant change in fasting blood sugar or haemoglobin levels as measured by A1c, the most reliable indicator of glucose control.

Table 21: Main conclusions from SRMAs of experimental studies on alcohol use, type II diabetes and related markers of blood glucose control

Study	N studies	Main Conclusions	Selection bias*
Schrieks et al., 2015 Incidence and glucose control	14 intervention studies	Moderate alcohol consumption does not influence insulin sensitivity but may decrease fasting insulin and haemoglobin concentrations among non-diabetic subjects.	None.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Genetic studies

Van de Luitgaarden et al. (2021) identified four MR studies examining the relationship between alcohol use and risk of type II diabetes. Most of these studies, predominantly those employing a single functional genetic variant as the genetic instrument, found no relationship between genetically predicted alcohol consumption level and risk of diabetes. One study using an Asian population, however, found a significantly positive linear relationship. One of the included studies did attempt to assess potential non-linearity, finding no evidence for J-shaped relationships. Higher quality MR studies employing a variety of genetic instruments (e.g. use of multiple single nucleotide polymorphisms [SNPs] to increase power and to allow

application of new MR methodologies to assess robustness of findings) and improved methodologies (e.g. non-linear analyses) are needed.

Table 22: Main conclusions from SRMAs of genetic studies on alcohol use and type II diabetes incidence and indicators of blood glucose control

Study	N studies	Main Conclusions	Selection bias*
Van de Luitgaarden et al., 2021 Incidence	4 MR studies	Null associations were reported for genetically predicted alcohol consumption and diabetes in most studies. More high quality MR studies (e.g. multiple SNPs, non-linear analyses) are needed.	None.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

Llamosas-Falcón et al. (2023) performed the most recent and comprehensive review of observational studies on this outcome with 55 cohort studies being identified and included. They used never drinkers as the reference group, adjusting for estimated effects of not using this reference in other studies. They estimated significant protection for low to moderate consumption among women but not men. In stratified analysis the protection for women was limited to those who were overweight or obese. Han (2020) performed a SRMA on eight cohort studies with Asian men. They report a J-shaped relationship between usual daily alcohol dose and future risk of developing type II diabetes. However, the reduced risk estimated at below three drinks per day (the breakeven point in the risk curve) was not significant whereas increased risk at higher levels was significant. No attempt was made to reduce selection bias so estimates of risk at every drinking level will likely be biased downwards.

Knott et al. (2015) identified 38 prospective studies on the association between typical alcohol consumption and risk of type II diabetes. In pooled meta-analysis of all studies they found evidence of reduced risk among moderate drinking women and non-Asian populations. This analysis was dominated by 33 studies with substantial selection bias (i.e. they had not accounted for former drinkers contaminating the abstainer reference group). In a sub-analysis of five studies using never drinkers as the reference (i.e. with reduced selection bias), no health benefits were observed.

Li et al. (2016) conducted a SRMA on 26 prospective observational studies. They report a J-shaped relationship with protective effects for light and moderate drinkers of both sexes

compared with nondrinkers and increased risk for heavier. However, this main analysis contains significant selection bias as never drinkers are not separated from former drinkers. Had occasional drinkers (up to one drink per day in this study) been used as the reference group, as is recommended by some investigators (e.g. Ortolá et al., 2024), moderate drinkers the decreased risk of type II diabetes would not have been significant.

Table 23: Main conclusions from SRMAs of observational studies on alcohol use and type II diabetes incidence, indicators of blood glucose control and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Llamosas-Falcón et al., 2023 Incidence	55 cohort studies	A reduced risk was estimated for women drinking light to moderate quantities per day but not for men. The beneficial effects were restricted to women with higher BMI.	Partial, never drinkers the reference.
Han 2020 Incidence	8 cohort studies	Non-significantly reduced diabetes risk in Asian men below three drinks per day and significantly increased risk above that level.	Substantial. Non-drinker reference.
Li et al., 2016 Incidence	26 prospective studies	Light and moderate alcohol consumption was associated with a lower risk of T2D, whereas heavy alcohol consumption was not related to the risk of T2D.	Substantial, Non-drinker reference.
Knott, Bell & Britton, 2015 Incidence	37 cohort studies 1 nested case-cohort study	Reductions in risk were absent in studies with a never-drinking abstention category or sampled an Asian population region.	Partial bias in sub-analysis with never drinkers.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Conclusions for blood glucose control and type II diabetes

Genetic studies find no significant associations either protective or harmful between level of alcohol use and risk of this outcome. While higher quality studies are needed, one of the included studies did explicitly test for J-shaped risk relationships, finding none. Short term experimental studies with non-diabetics provide mixed evidence with a negative effect of alcohol on insulin sensitivity and a possible beneficial effect for fasting insulin. However, a strong long-term RCT involving low-dose alcohol administration to people with type II diabetes found no evidence of significant impact on either fasting blood sugar or haemoglobin A1c, the most reliable long-term indicator of blood glucose control (Gepner et al, 2015).

The most recent, and least biased comprehensive review of observational studies (Llamosas-Falcón et al., 2023) finds no benefits of light to moderate consumption for men but some significant benefits for women who are overweight or obese. In the latter case, there was still some possibility of selection bias as lifetime abstention was not strictly defined.

CVD risk factors: 3. Arterial stiffness

Experimental studies

An apparent protective effect of light-to-moderate alcohol consumption was highlighted in three RCTs, in which experimental ingestion of alcohol was associated with reduced arterial stiffness in a SRMA by Del Giorno et al. (2022). These studies had small sample sizes (<20 individuals) of only young (<30 years), healthy, non-smoking men.

Hwang et al. (2021) conducted a far more comprehensive SRMA in which they identified 20 studies investigating acute (up to 13 hours) and short-term (up to several weeks) effects of different doses of alcohol, predominantly red wine. Most were randomised and all had some form of experimental control, either across or within subjects. The great majority of studies found either no effect of low to moderate alcohol doses or negative effects indicating increased arterial stiffness. Interestingly, de-alcoholised red wine and red grape juice had more beneficial effects than red wine in a few studies where these were compared. Consistently negative effects on endothelial functioning were observed for higher doses, usually at three or more drinks.

Table 24: Main conclusions from SRMAs of experimental studies on alcohol use and arterial stiffness incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Del Giorno et al., 2022	3 randomized trials	Light-to-moderate alcohol use associated with reduced arterial stiffness, while high doses accelerate arterial ageing. Given the heterogeneity of study methods, protective effects are likely but not certain. Most studies included healthy, young males, limiting generalizability.	None.
Hwang, Piano and Phillips, 2021	20 acute and short-term experiments	This review found that while light to moderate alcohol consumption may have minimal effects, heavy alcohol consumption was associated with increased arterial stiffness.	None.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

A SRMA by Del Giorno et al. (2022) included 10 observational studies with different designs. A J-shaped association between alcohol and vascular stiffness was found in five cross-sectional studies and evidence for positive associations in most others. Four other studies evidence arterial stiffness increasing with heavier drinking.

Hwang et al. (2021) conducted a SRMA in which 11 relevant observational studies were identified, which essentially used cross-sectional designs, in which endothelial functioning was assessed among individuals reporting different long-term drinking patterns. No or minimal steps were taken to identify former heavy drinkers among the comparison group of abstainers. Several of these studies assessed individuals with long histories of heavy alcohol consumption and nearly all found negative impacts on endothelial functioning. A few studied individuals with low or moderate daily consumption levels and found evidence of improved functioning compared with undefined "non-drinkers".

Table 25: Main conclusions from SRMAs of observational studies on alcohol use and arterial stiffness incidence and/or mortality risk and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Del Giorno et al., 2022	4 cohort, 6 cross-sectional studies	Light-to-moderate alcohol use associated with reduced arterial stiffness and increased with heavier drinking. Given the heterogeneity of study methods, "protective effects on arterial stiffness are likely but not certain".	Substantial, former and/or occasional drinker bias in control groups, mostly cross-sectional analyses.
Hwang, Piano and Phillips, 2021	11 cross-sectional studies	This review found that while light to moderate alcohol consumption may have minimal effects on FMD, heavy alcohol consumption was associated with a decrease in FMD. Most studies included healthy, young males, limiting generalizability.	Substantial, former and/or occasional drinker bias in control groups, mostly cross-sectional analyses.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Conclusions for arterial stiffness (endothelial function)

The most comprehensive SRMA by Hwang et al. (2021) identifying 20 experimental and 11 observational studies concluded minimal effects of low to moderate alcohol consumption and negative effects for higher consumption in relation to impact on endothelial function. The experimental studies in fact found almost as many negative as null impacts on indicators of arterial stiffness. Potentially beneficial ingredients in red wine were more effective in non-

alcoholic alternatives in some studies. While observational studies across both SRMAs found that low to moderate drinkers had improved functioning in comparison to non-drinkers, these were cross-sectional in design and were vulnerable to serious selection biases. Both SRMAs concluded further studies were needed on broader populations including women and people from older age groups.

(i) Coronary biomarkers

Experimental studies

We identified three SRMAs examining the effects of alcohol on a range of cardiac biomarkers in studies with strong experimental designs. These are short-term outcomes and indirect measures of cardiac risk. It is not certain that all the biomarkers canvassed in these studies are actually significant predictors of future heart disease. For example, there is some controversy as to whether HDL is a reliable indicator of future heart disease risk (Zakai et al., 2022).

Wilkens et al. (2022) conducted the most recent and comprehensive SRMA on alcohol use and lipid profiles. They identified 37 studies and reported a main finding of consistently positive associations with alcohol dosing and HDL. There were "a few studies" that found reductions in LDL. They concluded that alcohol use up to 60 g per day improved heart health. Notably, the authors of this SRMA declared funding from the Danish beer company Carlsberg.

Huang et al. (2017) conducted an SRMA on 31 experimental alcohol administration studies to look at the impact of low to moderate doses on various cardiac biomarkers with particular focus on "good" and "bad" cholesterol i.e. high-density and low-density lipoprotein (HDL and LDL). There were slight decreases in LDL of borderline significance ($p=0.05$) and significant increases in HDL.

Brien et al. (2011) conducted a comprehensive SRMA for the effects of alcohol dosage in 44 experimental studies on 13 cardiac biomarkers. They concluded alcohol had beneficial effects on heart health specifying positive results for three biomarkers, specifically higher HDL and adiponectin and lower fibrinogen. No significant effects were found for multiple other biomarkers including LDL.

Table 26: Main conclusions from SRMAs of experimental studies on alcohol use and coronary biomarkers and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Wilkens et al., 2022 Lipid profiles	37	Alcohol intake was positively associated good cholesterol (HDL). A few studies found lower levels of LDL. Authors concluded: "Up to 60 g/d alcohol can cause changes in lipoprotein subfractions and related mechanisms that could influence cardiovascular health."	None, not applicable.
Huang et al., 2017 Lipid profiles	31	Slight decrease in LDL (borderline significance), significant increase in HDL. Authors concluded: "Moderate alcohol consumption is causally related to lower risk of atherosclerosis through changes in lipid profiles and inflammation."	None, not applicable.
Brien et al., 2011 13 cardiac biomarkers	44	"Favourable changes in several cardiovascular biomarkers (higher HDL and adiponectin, lower fibrinogen) provide indirect pathophysiological support for a protective effect of moderate alcohol use on coronary heart disease." No effect for LDL.	None, not applicable.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Observational studies

Wilkens et al. (2022) identified 77 observational studies relating levels of alcohol use to cardiac biomarkers, particularly HDL and LDL. Their meta-analysis suggested consistent and positive associations with HDL but not LDL. These studies may have suffered from selection bias as no attempt was made to remove former or occasional drinkers from reference groups. The meta-analysis used abstinence or the lowest drinking category as the reference group in every case. Again, we note their declaration of funding received from Carlsberg.

Table 27: Main conclusions from SRMAs of observational studies on alcohol use and coronary biomarkers and steps taken to deal with selection bias

Study	N studies	Main Conclusions	Selection bias*
Wilkens et al., 2022 Lipid profiles	77 observational studies	Alcohol intake was associated with increased levels HDL. No consistent pattern for LDL. "Up to 60 g/d alcohol can cause changes in lipoprotein subfractions and related mechanisms that could influence cardiovascular health."	Substantial reference group bias, lowest alcohol consumption category used from each study.

* This refers only to our assessment of whether lifetime selection bias (Naimi et al., 2017) is considered i.e. whether the reference group is contaminated by former or occasional drinker bias.

Conclusions for cardiac biomarkers

Three SRMAs were identified which identified large numbers of both experimental and observational studies regarding the effects of low to moderate alcohol doses on cardiac biomarkers. The experimental and observational studies consistently found positive associations between alcohol and "good" cholesterol (HDL) and null or inconsistent results for "bad" cholesterol (LDL). One SRMA also reported beneficial effects on adiponectin and fibrinogen (Brien et al., 2011). No consistent or beneficial effects were found for the large majority of cardiac indicators examined, especially in Brien et al. (2011) who examined 13 different indicators. Furthermore, the most consistent finding of beneficial effects on HDL may not have any significance for future risk of heart disease as this has been repeatedly challenged as a reliable indicator. We conclude this area of research provides weak and inconsistent evidence for beneficial effects for a few indirect measures of future heart health.

Summary of Findings

Studies with CVD-related incidence or mortality outcomes

Only one randomised controlled trial (RCT) has been conducted with CVD-related incidence or mortality outcomes to date (Voskoboinik et al., 2020). This study found that reducing alcohol intake significantly reduced the recurrence of AF. In recent years there have been an increasing number of studies using genetic approaches, particularly Mendelian Randomisation (MR), which incorporate some of the strengths of an RCT in that genetic inheritance is, in effect, random and not influenced by lifestyle choices or sociodemographic characteristics. While more of these studies are required, two SRMAs of MR studies were identified which arguably provide the strongest evidence to determine potential impact of low to moderate alcohol consumption on CVD-related illnesses. The conclusions of these reviews were that there is no evidence for health benefits of light to moderate alcohol consumption in relation to ischaemic heart disease including myocardial infarction, unspecified stroke, atrial fibrillation, hypertension, heart failure, peripheral artery disease or unspecified CVD-related illnesses.

Observational studies were far more numerous with sometimes more than 100 being included in relevant SRMAs. As noted by almost all commentators, these are highly susceptible to the effects of systematic biases as well as other problems limiting certainty in conclusions of these studies such as residual confounding and reverse causation. Authors of identified SRMAs mostly concluded that low to moderate alcohol use was associated with

reduced risk of some CVD-related illnesses, in particular: IHD (including MI), ischaemic stroke, heart failure and unspecified CVD. However, the majority of SRMAs took no account of systematic bias so these conclusions are likely biased towards underestimation of risks at all levels of alcohol use. One exception is the SRMA by Zhao et al. (2017) which applied a strict criterion for lifetime abstention and mitigated the risk of lifetime systematic bias further by conducting a sub-analysis of younger cohorts followed up to old age. They found no significant protection against IHD for consumption of up to two drinks per day for this sub-group. Some other SRMAs, both for IHD and other outcomes, made partial attempts to reduce selection bias and some of these still concluded possible protective effects in relation to IHD, ischaemic stroke and heart failure. It is clearly necessary for more studies as well as SRMAs on alcohol and CVD-related illness to be conducted in which more effective steps are taken to reduce lifetime selection bias.

In relation to other CVD-related conditions, SRMAs of observational studies found no evidence of protective effects for low to moderate levels of alcohol consumption regardless of the extent to which steps were taken to mitigate selection bias. There was no evidence in these studies of protective effects in relation to haemorrhagic stroke, hypertension and atrial fibrillation. Because lifetime selection biases tend to make nondrinking comparison groups less healthy, estimates of the impact of low to moderate drinking on disease incidence and mortality will be underestimated in these studies i.e. in cases where SRMAs have concluded null effects it may be that the study designs mask small to moderate risks from alcohol use at low to moderate levels.

Table 28: Summary of SRMAs with results for experimental, genetic and/or observational studies on alcohol use and various CVD-related incidence or mortality outcomes

CVD outcomes	**SRMA study type**	**N SRMAs** (n studies)	**Degree of Bias**	**Health benefit**	**Overall conclusions**
Ischaemic heart disease (IHDand MI)	Experimental	0	-	-	No benefits in stronger studies.
	Genetic	2 (6)	None	No	
	Observational	11 (149)	Full for 6/11	Yes (7/9)	
Strokes (non-specific)	Experimental	0	-	-	No benefits in stronger studies.
	Genetic	1 (4)	None	No	
	Observational	2 (27)	Full	Mixed	
Ischaemic stroke	Experimental	0	-	-	Benefit but no bias free studies.
	Genetic	0	-	-	
	Observational	3 (25)	Full for 2/3	Yes (2/3)	
Haemorrhagic stroke	Experimental	0	-	-	No benefit but need bias free studies.
	Genetic	0	-	-	
	Observational	2 (11)	Full for 1/2	No	
Atrial fibrillation	Experimental	0	-	-	No benefits in weak or strong studies.
	Genetic	1 (2)	None	No	
	Observational	5 (13)	Full	No	
Heart failure	Experimental	0	-	-	No benefits in stronger studies.
	Genetic	1 (2)	None	No	
	Observational	4 (26)	Full 3/4	Yes (3/4)	
Hypertension	Experimental	0	-	-	No benefits in weak or strong studies.
	Genetic	1 (3)	None	No	
	Observational	6 (31)	Full 4/5	No (4/5)	
Peripheral artery disease	Experimental	0			No benefits in stronger studies.
	Genetic	1 (1)	None	No	
	Observational	1 (9)	Full 1/1	Yes (1/1)	
CVD (unspecified)	Experimental	0	-	-	No benefits in stronger studies.
	Genetic	1 (3)	None	No	
	Observational	3 (21)	Full	Yes (2/3)	

Studies of alcohol use and CVD risk factors

Evidence from experimental (short and longer-term outcomes), genetic and observational studies support the conclusions that a) there is a positive association between alcohol and blood pressure overall, and b) there are no protective effects at low levels of consumption. Furthermore, experimental trials with interventions to reduce drinking also show reductions in blood pressure among those who had previously been drinking two or more drinks daily.

Some evidence for limited health benefits in relation to glucose control and type II diabetes was provided by SRMAs for low to moderate alcohol use in both short-term experimental and some observational studies. The observational studies for diabetes suggested no

association for men but some beneficial associations for women who were overweight or obese. The most recent relevant SRMA took some partial steps to reduce lifetime selection bias. The experimental evidence reviewed in the identified SRMA (Schrieks et al., 2015) was restricted to short-term outcomes among individuals without diabetes (and the SRMA was funded by the alcohol industry). However, a unique two year-long RCT involving the administration of wine or water with an evening meal to an Israeli cohort with type II diabetes (identified in the SRMA by Roerecke and Rehm (2017)) found no evidence for significant improvement in haemoglobin levels as measured by A1c, the most reliable indicator of type II diabetes severity (Gepner et al, 2015). The genetic studies available also found no protective effects for alcohol and type II diabetes.

Stronger study designs, namely experimental and genetic studies, mostly found negative effects of low to moderate alcohol use on the associated risk factor of arterial stiffness (otherwise known as endothelial functioning). Some studies included in these SRMAs noted that grape juice and/or de-alcoholised red wine were associated with similar or improved outcomes compared with wine. Observational studies, mostly cross-sectional, tended to find beneficial associations for endothelial function. However, these took no account of lifetime selection bias.

We conclude there is relatively strong evidence, across multiple types of study, against the hypothesis that low to moderate alcohol use has beneficial effects in relation to blood pressure, blood glucose control or arterial stiffness. There was strong and consistent evidence across multiple study designs for adverse effects from higher levels of alcohol consumption on blood pressure, blood glucose control and arterial stiffness.

Table 29: Summary of SRMAs with results for experimental, genetic and/or observational studies on alcohol use and various proven CVD risk factors

CVD outcomes	**SRMA study type**	**N SRMAs** (n studies)	**Degree of Bias**	**Health benefit**	**Overall conclusions**
Blood pressure	Experimental	2 (36)	None	No	Negative effects, no safe threshold.
	Genetic	1 (5)	None	No	
	Observational	1 (7)	Full	No	
Type II Diabetes	Experimental	1 (14)	None	Possible	Possible benefits for overweight women.
	Genetic	1 (4)	None	No	
	Observational	4 (55)	Partial	For some women	
Arterial stiffness	Experimental	2 (20)	None	No	Stronger studies find no benefits.
	Genetic	0	-	No	
	Observational	2 (11)	Full	Yes	

Studies of alcohol use and indirect CVD biomarkers

SRMAs of the many experimental and observational studies on these indirect markers of CVD risk found positive associations between alcohol and "good" cholesterol (HDL) and no or inconsistent results for "bad" cholesterol (LDL). HDL, however, is not universally accepted as a reliable predictor of future heart disease. A comprehensive though now dated SRMA by Brien et al. (2011) found evidence of potential benefits for only two out of a further 11 cardiac biomarkers, namely adiponectin and fibrinogen. There is also evidence that equivalent benefits can be gained from consuming some kinds of fruit, particularly grapes (e.g. Weaver et al., 2021). We conclude this area of research provides weak and inconsistent evidence for beneficial effects for a few indirect measures of future heart health.

Table 30: Summary of SRMAs with results for experimental, genetic and/or observational studies on alcohol use and various indirect CVD biomarkers

CVD biomarkers	**SRMA study type**	**N SRMAs** (n studies)	**Degree of Bias**	**Health benefit**	**Overall conclusions**
HDL, LDL, adiponectin & fibrinogen	Experimental	44	None	For 3/13 indicators	Weak evidence for minor benefits, not from alcohol.
	Genetic	0	-	-	
	Observational	77	Full	Yes	

Conclusions

Our major conclusion is that there is now strong evidence for scepticism about the hypothesis that alcohol use in moderation can protect against heart disease. The classic J-shaped curve used to describe the fall and rise of mortality risk with level of alcohol use is

absent in both genetic and observational studies with stronger research designs. Furthermore, the widespread failure of observational studies (and many SRMAs of these) to take account of lifetime selection bias means that the extent of disease and mortality risk from alcohol use at any level is likely underestimated. In the majority of these studies, relatively healthy people who are well enough to drink alcohol are compared with a relatively unhealthy group of "non-drinkers" many of whom have quit or cut down for health reasons.

There is a new wave of research in this area employing genetic study designs. The more sophisticated MR studies (e.g. Biddinger et al., 2022; Millwood et al., 2019) find that the risk of CVD illness increases in a linear way with level of alcohol consumption and with no safe threshold. We note that more recent genetic studies not yet included in an SRMA and using mortality outcomes also support this conclusion (e.g. Millwood et al., 2023; Kassaw et al., 2024). The SRMA's of genetic studies reviewed here, however, tend to conclude there are either null or harmful overall associations between alcohol use and CVD risk.

At higher levels of alcohol consumption there was universal and consistent evidence of adverse effects on biomarkers, risk factors and the incidence of CVD.

Recommendations for future research

1. More studies are needed using genetic methodologies such as MR and which conduct analyses to test for potential "non-linear" i.e. J-shaped risk relationships.

2. More observational studies with prospective designs are needed in which strict measures are taken to reduce lifetime selection biases that are prevalent in the existing literature. Such steps should include: a) a strict definition of lifetime abstention b) the reallocation of former drinkers into drinking groups, c) the recruitment of participants at younger ages (e.g. less than 50 years) before selection bias has fully developed. An additional and promising approach is to exclude all current abstainers from the comparison group and employ people who have consistently drunk only occasionally e.g. at no more than one or two drinks per week as the reference to compare drinkers against (Ortolá et al., 2024).

3. We recommend the development of further, innovative RCT trials involving daily low-dose alcohol administration versus no alcohol control conditions and/or intervention trials aimed at reducing consumption of light to moderate drinkers (e.g. Voskoboinik et al., 2020). These could assess intermediate outcomes (blood sugar, blood pressure, endothelial function) and, ideally, also longer term morbidity and mortality. Doing trials of secondary prevention (e.g., whose outcome might include recurrent IHD events) randomizing non-

dependent drinkers to very low or no consumption vs. usual consumption would seem to be more feasible and timely than primary prevention trials.

4. Estimates of the Global Burden of Disease of alcohol should at the very least separate out estimated harms from estimated benefits if cardio-protection is assumed. We suggest that grounds for scepticism about cardio-protection are now strong and it is misleading therefore to present "net" effects of alcohol use on disease incidence and mortality. Such a practice masks the adverse effects of alcohol on health.

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