DRINKING AND CARDIOVASCULAR DISEASE

IARD Health Reviews offer an overview of scientific literature on the relationship between alcohol consumption and health outcomes and provide the reader with a bibliography that refers to original peer-reviewed research on each topic. The Reviews attempt to present the balance of the available evidence. They do not necessarily reflect the views of IARD or its sponsoring companies.

Last Reviewed: July 2018

Background

Cardiovascular disease (CVD) encompasses several distinct conditions involving the heart and blood vessels and is the leading cause of morbidity and mortality worldwide, particularly in middle- and high-income countries. Globally, 32% of all deaths are attributed to CVD [1].

Some of the known risk factors for CVD include health-related behaviors, existing health conditions or family history, and genetic traits. These are often categorized into modifiable and nonmodifiable risk factors:

Modifiable risk factors for CVD [2, 3]	Non-modifiable risk factors for CVD [2, 3]
Unhealthy diet Smoking Overweight or obesity Alcohol consumption Physical inactivity	Age Gender Race/ethnicity Socioeconomic status Family history
Diabetes and hypertension	

This IARD Health Review focuses on the role of alcohol consumption as a risk factor for CVD.

This Health Review presents the findings from meta-analyses (a type of study which pools multiple individual studies), large prospective cohort and case-control studies, and experimental studies published within the past 10 years. We give priority to the results of meta-analyses and pooled cohort studies over presenting the results of individual studies when possible. When there is limited research available on a given CVD outcome, we may include the results from individual studies and/or studies pre-dating the prior 10-year timeframe. The CVD conditions and outcomes described in this Review reflect those areas where there is a sufficient body of research, which could be considered more developed than exploratory research, on the association between alcohol consumption and the CVD outcome.

A glossary of key cardiovascular terms can be found on page 11.

Summary of the Evidence

OVERVIEW

Over the past five decades, hundreds of studies have examined the relationship between alcohol consumption and total CVD or coronary heart disease (CHD) risk and, while findings vary across studies, the majority of large studies – including eight out of nine meta-analyses published since 2008 – have found that risk is lower for individuals who are light or moderate drinkers than for those who do not drink at all [4-11] and those who drink heavily [4, 6, 7].

A similar non-linear relationship, where risk is lower for light or moderate drinkers, has also been found in studies examining the association between alcohol consumption and all-cause mortality [4, 11, 12]. The findings for all-cause mortality are strongly influenced by the association between alcohol and CVD, which is the leading cause of morbidity and mortality worldwide [1].

One of the nine recently published meta-analyses of CHD mortality and alcohol consumption concluded that this non-linear association was not observed in "higher quality studies", as determined by the authors, or in studies conducted with participants younger than 55 years old at the beginning of the study period [13]. A meta-analysis of all-cause mortality and alcohol consumption by the same authors reached a similar conclusion [14].

While most systematic reviews and meta-analyses find a lower risk for CVD or CHD associated with low-to-moderate alcohol consumption, this relationship has been challenged on methodological grounds [13, 15, 16] including issues related to observational studies. These are discussed in detail in the Methodological Issues section of this Review.

LIGHT, MODERATE, AND HEAVY DRINKING DEFINITIONS

There are no universally accepted definitions for drinking levels and this is evident in the wide variation between definitions provided by national guidelines, as well as differences in standard national drink sizes. Many research studies refer to an assumed standard drink or to drinking levels associated with national guidelines (for example, Bell et. al 2017 use previous UK drinking guidelines to differentiate between moderate and heavy).

The terms light, moderate, and heavy drinking, as defined by the studies included in this Health Review, vary widely in their definitions. For example, moderate drinking can refer to: one to two drinks per day, one drink for women and two drinks for men per day, 12.5 to 25 g of pure alcohol consumed per day, 10 to 20 g per day, or up to 24 g per day.

When describing results of specific studies, this Health Review reports drinking level information as provided by the referenced study. When describing overall results across several studies, this Health Review may use light or moderate drinking to broadly indicate less than or up to one to two drinks per day and heavy drinking to broadly indicate more than two or three drinks per day.

DRINKING PATTERNS AND RISK

For some cardiovascular conditions, risk increases linearly with increasing alcohol consumption and a statistically significant increase in risk is associated with heavy drinking. Studies reporting a linear association describe the relationship between drinking and risk for the following conditions.

- **Hemorrhagic stroke** – A linear relationship between drinking levels and hemorrhagic stroke has been described in a recent meta-analysis finding increased risk for heavier drinkers but no association with light or moderate drinking [17]. These results are generally consistent with a 2010 meta-analysis that found evidence of a similar dose–response relationship for hemorrhagic stroke mortality for both men and women [18].
- **Atrial fibrillation** (an abnormal cardiac rhythm) – Four meta-analyses published since 2010 [19-22] have consistently reported a linear association between alcohol consumption and atrial fibrillation (AF), with two of these studies showing an increase in risk beginning at one to two drinks per day compared with no drinking [20, 22]. Sex-specific differences have been observed for moderate drinkers (one to two drinks per day) where men had an increase in risk, but women did not [19]. The association between low-dose alcohol consumption (less than one drink per day) and AF is less clear, which makes it difficult to determine whether the relationship is truly linear or curvilinear.
- **Cardiomyopathy** – Although there are limited and conflicting data on factors that may contribute to alcoholic cardiomyopathy, evidence indicates that chronic heavy drinking over several years can be a risk factor [23-25]. Light and moderate drinking has not been associated with either increased or reduced risk of cardiomyopathy.
- **Hypertension among men** – Studies have found differences between the sexes in the relationship between alcohol and hypertension. For men, there is evidence of a linear association between alcohol consumption and risk above 30 grams of pure alcohol per day, while for women the relationship does not appear to be linear [26, 28]; hypertension among women is summarized in the next section.
  - **A meta-analysis** of controlled trials [29] found a linear relationship between alcohol and hypertension above a threshold of two drinks per day. For those drinking below this threshold, reducing alcohol intake did not appear to be associated with a decrease in blood pressure, which suggests that lower levels do not increase blood pressure.

- **For other cardiovascular conditions and for total CVD, alcohol consumption has a nonlinear, J-shaped association** with risk where light-to-moderate drinking is associated with lower risk than both not drinking at all and heavy drinking. Studies reporting a nonlinear relationship between drinking and risk include:

- **Total CVD** – Studies have found an association between light-to-moderate drinking and reduced risk for total CVD mortality compared with nondrinkers [4], including one meta-analysis examining this relationship exclusively among women [11]. Research indicates that this relationship also holds for populations with pre-existing hypertension [10]. In most studies, risk is increased for heavy drinkers compared to nondrinkers, but the increase does not reach statistical significance across all studies. This may be due to the limited number of heavy drinkers in some studies. Two large cohort studies support these results finding that lifetime abstainers, former drinkers, and heavy drinkers had an increased risk of CVD compared with light [30] or moderate drinkers [31].
  - **The main effects** of alcohol consumption on CVD risk have recently been explored in a relatively new approach, Mendelian randomization (MR); see sidebar for a description of the MR approach. Some studies adopting this methodology find no effect of alcohol consumption, defined by carriage of a mutation in an alcohol-metabolizing gene, on CVD risk [31, 32] while others find both adverse and beneficial effects on some CVD risk factors [33, 34].

- **Ischemic heart disease (IHD) or coronary heart disease (CHD)** – Seven out of eight recent meta-analyses documented a reduced risk of IHD/CHD among light-to-moderate drinkers compared with nondrinkers [4, 6-9, 35], including one meta-analysis examining this relationship exclusively among women [11]. However, one of these studies [13] concluded that a reduced risk was not apparent when analysis was restricted to "higher quality studies", as determined by the authors. Three of these meta-analyses found an increased risk associated with heavy drinking [4, 6, 7].

  The most common manifestations of IHD are myocardial infarction (heart attack) and heart failure.

- **Myocardial Infarction (MI)** – A recent UK cohort study of almost two million individuals found increased risk associated with not drinking and heavy drinking compared with moderate drinking [30]. A 2016 meta-analysis found an increase in risk of an MI event in the first hour following alcohol consumption, including moderate consumption. Among events occurring later than 24 hours after consumption, however, light and moderate drinking – but not heavy drinking – was associated with a reduced risk of MI [36]. A prospective cohort study conducted in 12 predominantly lower-income countries found similar results: low and moderate intake (up to two drinks for men and one drink per day for women) was associated with reduced MI risk compared with never drinkers [37].

- **Heart failure** – Three recent meta-analyses have examined the association between alcohol consumption and heart failure since 2008. All three have reported lower risk associated with light drinking (up to one drink per day) compared with abstaining from alcohol [38-40], and two of out of three [39, 40] also found lower risk associated with moderate drinking (up to two drinks per day). Only one study separated former drinkers from other nondrinkers and reported an increased risk of heart failure among former drinkers [38].

- **Ischemic stroke** – Several recent studies have found that light-to-moderate drinking has been associated with significantly reduced risk of ischemic stroke [17, 18, 31, 42] and total stroke [42], while heavy drinking has been associated with increased risk of ischemic and hemorrhagic stroke [17], and total stroke [42], compared with nondrinkers.

- **Hypertension among women** – Among women, recent meta-analyses have found a decreased risk of hypertension with alcohol consumption of less than 10 g per day, whereas a significantly increased risk of hypertension was indicated with an alcohol consumption of between 31 and 40 g per day [26, 27].

  - **However,** at the time of writing of this Health Review, a newly-published systematic review and meta-analysis of studies examining the association between alcohol consumption and hypertension failed to find evidence of a

decreased risk among women who consumed between one and two drinks per day (<= 24g per day) but did confirm previous findings of an increased risk above two drinks per day [43].

The potential protective effects of moderate drinking may be diminished or entirely eliminated by occasional heavy episodic drinking (HED).

Heavy episodic drinking (binge drinking) has been associated with increased risk of:

- **Acute myocardial infarction (MI)** – Mortality risk was two-times higher among heavy episodic drinkers than among drinkers who did not report HED in a 2005 cohort study of patients with prior history of an acute MI incident [42].
- **Atrial fibrillation** – Risk was found to be higher among current drinkers who reported HED than among those who did not, even when average alcohol consumption and frequency of consumption were accounted for [20].
- **Ischemic heart disease (IHD)** – Risk of IHD among moderate drinkers with HED occasions was 45% higher than among moderate drinkers without such occasions [43]. These results were duplicated in a later study with a U.S. national sample [44] and in a meta-analysis [45]. A 2008 meta-analysis reached a similar conclusion, finding a reduced risk of CHD among regular (i.e. no HED) drinkers and an increased risk among irregular heavy drinkers [9].

MENDELIAN RANDOMIZATION

A new approach to testing causal relationships between alcohol consumption and CVD uses an analytical tool called Mendelian randomization (MR) to overcome some of the challenges of observational studies. An MR approach uses the presence or absence of a genetic variant in one or more genotypes associated with drinking as a proxy for alcohol use.

Since genetic variants occur at conception, are randomly distributed across a population, and are independent of other factors that could be associated with cardiovascular health, individuals with a given genetic variant can be considered as having been randomly assigned to a "group"; this allows for a nearly experimental comparison between genotype groups.

Thus, this type of study allows researchers to test a hypothesis of a causal relationship between drinking alcohol and CVD or biomarkers of CVD risk factors.

There are several important considerations in assessing whether an MR approach is appropriate [48], some of which include the following:

- The study population needs to be sufficiently large.
- The genetic variant must be strongly associated with alcohol consumption: some variants are more strongly associated with drinking than others.
- Multiple dimensions of drinking behavior (any drinking, average drinking volume, and heavy episodic drinking) need to be assessed because failure to consider these multiple dimensions in the analysis may lead to erroneous conclusions. For example, it has been demonstrated that moderate drinkers who report HED have a higher risk for cardiovascular diseases than moderate drinkers who do not engage in HED; therefore, failing to account for HED could mask significant differences in risk within moderate drinkers [49].
- Individuals with the genetic variant may adapt their drinking behavior over time.

Finally, MR is one of several methods of assessing or supporting causal relationships in epidemiologic research; other procedures include randomized controlled trials, natural experiments, and certain types of statistical analysis (such as propensity score matching, time series analysis, and structural equation modelling). The results of an MR study cannot supplant existing research but should be considered one part of the body of evidence coming from epidemiological and experimental research [48, 49].

AMONG INDIVIDUALS AT INCREASED RISK FOR CVD

Studies have indicated that light-to-moderate alcohol consumption is associated with improved CVD outcomes (a lower risk of progression to CVD or premature death compared with abstainers or heavy drinkers) among individuals with health conditions that are independently associated with CVD, such as diabetes, metabolic syndrome (MetS), and hypertension.

- A meta-analysis of studies examining CVD outcomes among patients with hypertension found that low-to moderate alcohol consumption (median consumption less than 30g per day) was associated with significantly reduced risk of CVD and all-cause mortality compared with abstaining or occasional drinking [10].
- Similarly, a meta-analysis of studies examining patients with Type 2 diabetes found that alcohol consumption up to 18g per day was associated with reduced coronary heart disease (CHD) incidence and all-cause mortality risk [50].
- Among individuals with MetS, one recent meta-analysis has shown that adherence to a Mediterranean-type diet that typically includes "moderate daily alcohol consumption" was associated with lower prevalence of MetS, progression of MetS, and several measures of individual MetS components [51]. The independent effect of alcohol on these outcomes was not assessed.

Individual genetic differences in ethanol metabolism may modify the effect of alcohol on CVD risk. For example, men with slow alcohol metabolism appear to have a lower risk of CHD than those with fast alcohol metabolism at moderate drinking levels [52], potentially through cardiometabolic risk factors such as glycemic (blood sugar) control [53] or an improved lipid profile [54].

BIOLOGICAL MECHANISMS

While exact mechanisms are not fully understood, the effect of alcohol on cardiovascular conditions appears to be mediated through interrelated lipid, hemostatic, and inflammatory factors that may ultimately influence several characteristics of heart disease: inflammation, hypercoagulability, hypercholesterolemia, and hyperglycemia/hyperinsulinemia [55].

Several biomarkers have been examined in experimental research studies and in three recent meta-analyses of such studies [56-58]. These studies have demonstrated that moderate alcohol consumption, compared with a no-alcohol control group, was associated with:

- Higher levels of high-density lipoprotein (HDL) or "good" cholesterol [56, 57]
- Higher levels of apolipoprotein A1 [57]
- Higher levels of adiponectin [56, 57]
- Lower levels of low-density lipoprotein cholesterol [57]
- Reduced fibrinogen levels [54, 56, 57]
- Reduced interleukin 6 [57]
- Decreased fasting insulin (an indicator of insulin sensitivity in healthy individuals) among both men and women and improved insulin sensitivity among women [58]

ALCOHOL BEVERAGE TYPE

Moderate alcohol consumption has been shown to have an association with reduced risk of CVD and with improved CVD biomarkers [56, 59, 60] across multiple beverage types [61, 62].

- Evidence of improvement in CVD biomarkers is strongest for the effects of ethanol over beverage specific constituents [60, 63].
- Research from clinical trials suggests that antioxidants, such as resveratrol and other polyphenols (found especially in wine) or B-vitamins (found especially in beer), may confer additional cardiovascular benefits beyond those from ethanol [64-66].
- Beverage preference may be associated with lifestyle risk factors and behaviors [67-69] that may confound the relationship with health outcomes. It should be noted that most studies examine the relationship between alcohol consumption and CVD risk by combining all types of alcohol – beer, wine, and spirits – into a single measure, and a great deal of the research evidence on drinking and CVD comes from these all-inclusive estimates which aim to study the role of ethanol.

Methodological issues

There has been discussion in the research literature about the inherent limitations of epidemiological studies, the measurement of alcohol consumption, the role of study quality, and the impact of these limitations on the interpretation of research that has focused on the association between alcohol consumption and CVD.

Researchers have raised several important issues that could potentially bias a study's results by producing erroneous findings and leading to incorrect conclusions about the effects of moderate drinking on cardiovascular health. Three of these issues are described briefly below.

CLASSIFICATION ERRORS

The way in which drinkers and nondrinkers are classified in studies may have an impact on observed outcomes for CVD. Some examples of different types of classification errors include the following:

- The "sick quitter" hypothesis was first described in 1988 and postulates that many former drinkers have stopped drinking for health reasons [70]. If these individuals are classified as nondrinkers in the same group as lifetime abstainers, then any existing poor health conditions may make it appear that abstainers are at higher risk of CVD than moderate drinkers. Some studies have claimed that this bias applies to all studies combining lifetime abstainers and occasional and former drinkers [13, 16, 71]. This effect is sometimes referred to as abstainer bias.
  - Recent studies have accounted for this potential source of bias by separating former drinkers from lifetime abstainers or testing whether there are differences in risk estimates between these two groups before combining them into a single nondrinker category [4, 31, 39, 47, 72, 73].
  - Furthermore, there is no generally accepted approach to dealing with potential abstainer bias and this inconsistency results in different researchers choosing different reference groups in their analysis (such as lifetime abstainers, occasional drinkers, or moderate drinkers).

- There is little consistency in the definitions used across research studies for what constitutes light, moderate, and heavy alcohol consumption. Definitions may be based on different levels set for average daily or weekly volume, average frequency of alcohol consumption, or a combination. This lack of consensus on what constitutes moderate or heavy drinking can diminish comparability across different studies and may make it difficult to combine them into a pooled analysis.
- Self-reported alcohol consumption data is subject to underestimation due to recall errors (difficulty with accurately remembering past behavior) and social desirability bias (the desire to provide a more favorable response). The latter may be especially relevant for surveys asking questions about potentially sensitive information, such as alcohol consumption. If respondents have underreported their consumption, then the cardiovascular benefits or risks associated with light or moderate drinking may actually apply to higher average quantities of alcohol than assumed.
  - There are methods for minimizing potential underestimation errors. Some studies collect multiple measures of alcohol consumption over time, or other information which may be used to identify and separate respondents who likely under-report their consumption from other respondents [74, 75].

CONFOUNDING

Other healthy behaviors that coincide with moderate drinking, and not moderate drinking as such, may explain the observed reduced risk for CVD among moderate drinkers.

This potential source of error is sometimes referred to as confounding bias.

Many factors may be associated with both drinking behavior and CVD outcomes and should be accounted for in a study's design or in the data analysis as much as possible.

- These include: individual factors, such as gender, race and ethnicity; genetic and physiological factors; behavioral factors, such as smoking, diet, and physical activity; social and economic factors; and existing health conditions.
- Because epidemiological studies are unable to control for all potential confounders, the possibility that the results could be explained by residual confounding cannot be excluded, and the results of observational studies should be interpreted with some caution.

The question of whether or not moderate drinking is simply an indicator of an overall healthy lifestyle is particularly relevant to the discussion of moderate drinking, CVD risk, and potential confounding bias.

- Moderate alcohol consumption has been shown to coincide with other healthy lifestyle behaviors such as maintaining a healthy body weight, regular exercise, and sufficient sleep [76] or healthy diet [77]. Research has shown that individuals adopting multiple healthy behaviors have significantly lower risk of death from all causes [11, 77-79] and CVD [11, 77, 79, 80].
- Healthy behaviors are also linked with socioeconomic status [81] and individual socioeconomic factors, such as educational attainment [82-84] or occupational class [85], and socioeconomic status are independently associated with CVD and all-cause mortality risk [81, 86].
- For these reasons, some researchers have hypothesized that moderate drinking is simply an indicator of other healthy behaviors unrelated to alcohol [13].
- Some studies attempt to isolate the effects of moderate drinking from other lifestyle behaviors and have found that the J-shaped curve still holds [72, 87-89] .
- Several research approaches can minimize potential confounding bias. These include randomized controlled trials, natural experiments, Mendelian randomization, and certain advanced statistical analysis techniques.

SELECTION BIAS

Selection bias may occur when individuals participating in a research study are not representative of the general or targeted population, and may result in a distortion (underestimation or overestimation) of the relationship between alcohol consumption and CVD risk.

- Healthier individuals may be more likely to participate in a research study and continue participating throughout the course of the study than individuals with health issues. This is likely to result in a lower prevalence of CVD outcomes in the study population, which may distort CVD risk in this sample. In addition, risky or heavy drinkers may be less likely to participate in a study due to social isolation, homelessness, or mental illness.

- However, selection of the study population from a source population does not necessarily produce a selection bias that distorts the measure of association. Participants selected for case-control studies and cohort studies do not have to be representative of the general population for an association to be internally valid. Thus, researchers are able to study select groups and have the expectation that that results will be meaningful (for example, nurses participating in the Nurses' Health Study). This is why the results of large, long-duration studies are important parts of the evidence; these types of studies can focus on the effects of alcohol on CVD risk by minimizing differences in other factors (socioeconomic or lifestyle) among participants.

- Another type of selection bias relates to survival bias, or unavailability of drinkers who have died prematurely from an alcohol-related cause for participation in a research study. This bias assumes that individuals who die at younger ages are more likely to be drinkers than non-drinkers because alcohol is a leading risk factor for the causes of death that are more prevalent among younger individuals (unintentional injuries and violence) [15].

- **Non-response bias** is a type of selection bias that occurs when there is a significant difference between those who respond to a survey and those who do not. This can occur when people refuse to participate in a study, or forget to return survey responses. Problem drinkers may be less inclined to respond to surveys regarding alcohol consumption compared to occasional drinkers. A high non-response rate can lead to a small or less random sample that affects how well the data represents the population being surveyed.

- **Loss to follow-up** refers to a subject's initial participation in a study and subsequent loss due to dropping out of the study, relocating from study setting, or death. If loss of participants varies between study groups and dropouts are systematically different from those who do not drop out, it can bias estimates of the relationship between alcohol consumption and CVD risk.

Glossary

Cardiovascular disease (CVD) encompasses a number of distinct conditions involving the circulatory system (heart and blood vessels). Some of the main types of CVD or CVD-related conditions include:

- **Ischemic heart disease,** also known as coronary artery disease or coronary heart disease (CHD), involves reduced blood supply to the heart, most often due to atherosclerosis, or thickening of arterial walls. Ischemic heart disease, coronary heart disease, and coronary artery disease are used interchangeably in the research literature.
- **Hypertension** refers to chronic elevated blood pressure defined as systolic blood pressure above 140 mm/Hg or diastolic pressure above 90 mm/Hg. Uncontrolled hypertension may lead to cardiovascular complications including heart failure, ischemic/coronary artery disease, atrial fibrillations, and stroke.
- **Atrial fibrillation** is a common type of cardiac arrhythmia, or irregular heartbeat, and is a risk factor for stroke and heart failure.
- **Stroke** is the result of an acute blockage of blood flow to the brain and includes two types: ischemic stroke (resulting from lack of blood flow either from a blood clot breaking off somewhere else in the body and lodging in an artery in the brain or from a plaque rupturing in the brain's arteries and blocking a blood vessel) and hemorrhagic stroke (resulting from bleeding in the brain).
- **Heart failure**, which can be chronic or acute, results from the heart's inability to pump and circulate sufficient blood to the body.
- **Cardiomyopathy** refers to an abnormally enlarged, thickened, or stiffened heart muscle, or myocardium, resulting in a weakened heart muscle and diminished blood circulation; this is a chronic condition that can lead to cardiac arrhythmia or heart failure.
- **Myocardial infarction**, more commonly referred to as a heart attack, is the result of an obstruction of the blood supply, and oxygen, leading to damage of myocardium (heart muscle).
- **Peripheral arterial disease** is a more pervasive form of atherosclerosis, restricting blood flow to the extremities.

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