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Effect of alcohol on blood pressure (Review)

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[Intervention Review]

Effect of alcohol on blood pressure

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ABSTRACT

Background

Alcohol is consumed by over 2 billion people worldwide. It is a common substance of abuse and its use can lead to more than 200 disorders including hypertension. Alcohol has both acute and chronic effects on blood pressure. This review aimed to quantify the acute effects of different doses of alcohol over time on blood pressure and heart rate in an adult population.

Objectives

Primary objective

To determine short-term dose-related effects of alcohol versus placebo on systolic blood pressure and diastolic blood pressure in healthy and hypertensive adults over 18 years of age.

Secondary objective

To determine short-term dose-related effects of alcohol versus placebo on heart rate in healthy and hypertensive adults over 18 years of age.

Search methods

The Cochrane Hypertension Information Specialist searched the following databases for randomised controlled trials up to March 2019: the Cochrane Hypertension Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 2), in the Cochrane Library; MEDLINE (from 1946); Embase (from 1974); the World Health Organization International Clinical Trials Registry Platform; and ClinicalTrials.gov. We also contacted authors of relevant articles regarding further published and unpublished work. These searches had no language restrictions.

Selection criteria

Randomised controlled trials (RCTs) comparing effects of a single dose of alcohol versus placebo on blood pressure (BP) or heart rate (HR) in adults (≥ 18 years of age).

Data collection and analysis

Two review authors (ST and CT) independently extracted data and assessed the quality of included studies. We also contacted trial authors for missing or unclear information. Mean difference (MD) from placebo with 95% confidence interval (CI) was the outcome measure, and a fixed-effect model was used to combine effect sizes across studies.

Main results

We included 32 RCTs involving 767 participants. Most of the study participants were male (N = 642) and were healthy. The mean age of participants was 33 years, and mean body weight was 78 kilograms.

Low-dose alcohol (< 14 g) within six hours (2 RCTs, N = 28) did not affect BP but did increase HR by 5.1 bpm (95% CI 1.9 to 8.2) (moderate-certainty evidence).

Medium-dose alcohol (14 to 28 g) within six hours (10 RCTs, N = 149) decreased systolic blood pressure (SBP) by 5.6 mmHg (95% CI -8.3 to -3.0) and diastolic blood pressure (DBP) by 4.0 mmHg (95% CI -6.0 to -2.0) and increased HR by 4.6 bpm (95% CI 3.1 to 6.1) (moderate-certainty evidence for all).

Medium-dose alcohol within 7 to 12 hours (4 RCTs, N = 54) did not affect BP or HR.

Medium-dose alcohol > 13 hours after consumption (4 RCTs, N = 66) did not affect BP or HR.

High-dose alcohol (> 30 g) within six hours (16 RCTs, N = 418) decreased SBP by 3.5 mmHg (95% CI -6.0 to -1.0), decreased DBP by 1.9 mmHg (95% CI-3.9 to 0.04), and increased HR by 5.8 bpm (95% CI 4.0 to 7.5). The certainty of evidence was moderate for SBP and HR, and was low for DBP.

High-dose alcohol within 7 to 12 hours of consumption (3 RCTs, N = 54) decreased SBP by 3.7 mmHg (95% CI -7.0 to -0.5) and DBP by 1.7 mmHg (95% CI –4.6 to 1.8) and increased HR by 6.2 bpm (95% CI 3.0 to 9.3). The certainty of evidence was moderate for SBP and HR, and low for DBP.

High-dose alcohol ≥ 13 hours after consumption (4 RCTs, N = 154) increased SBP by 3.7 mmHg (95% CI 2.3 to 5.1), DBP by 2.4 mmHg (95% CI 0.2 to 4.5), and HR by 2.7 bpm (95% CI 0.8 to 4.6) (moderate-certainty evidence for all).

Authors' conclusions

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. Findings of this review are relevant mainly to healthy males, as only small numbers of women were included in the included trials.

PLAIN LANGUAGE SUMMARY

Alcohol has a biphasic effect on blood pressure and increases heart rate

Review question

We reviewed available evidence about the short-term effects of different doses of alcoholic drinks compared to non-alcoholic drinks on blood pressure and heart rate in adults (≥ 18 years) with both normal and raised blood pressure.

Background

Drinking excessive alcohol is considered one of the most common causes of raised blood pressure. We wanted to quantify the effects of a single dose of alcohol on blood pressure and heart rate within 24 hours of consumption.

Study characteristics

We included 32 randomised controlled trials involving 767 participants published up to March 2019. Although these trials included adults from 18 to 96 years of age with various health conditions, most study participants were young healthy males. The source of funding was not reported for a majority of the studies.

Key results

For low doses of alcohol, we found that one glass of alcohol had little to no effect on blood pressure and increased heart rate within six hours of drinking.

We are moderately certain that medium-dose alcohol decreased blood pressure and increased heart rate within six hours of consumption. We did not see any significant change in blood pressure or heart rate after that, but the evidence was limited.

We are also moderately certain that high-dose alcohol decreased blood pressure within six hours, and the effect lasted up to 12 hours. After that, blood pressure was found to be increased. Heart rate increased significantly after alcohol consumption and remained increased at all times measured.

Thus alcohol decreases blood pressure initially (up to 12 hours after ingestion) and increases blood pressure after that. Alcohol consistently increases heart rate at all times within 24 hours of consumption.

SUMMARY OF FINDINGS

Summary of findings 1. Effect of high-dose alcohol compared to placebo

Effect of high-dose alcohol compared to placebo

Patient or population: adult participants
Setting: ambulatory
Intervention: high-dose alcohol (> 30 g)
Comparison: placebo

Outcomes	Participants (RCTs)	Certainty of the evidence (GRADE)	Mean difference of high-dose alcohol compared to placebo* (95% CI)
Systolic blood pressure - ≤ 6 hours	418 (16)	⊕⊕⊕⊖ Moderate[a]	-3.5 mmHg [-6 to -0.5]
Systolic blood pressure - 7 to 12 hours	54 (3)	⊕⊕⊕⊖ Moderate[a]	-3.7 mmHg [-6.9 to -0.5]
Systolic blood pressure - ≥ 13 hours	154 (4)	⊕⊕⊕⊖ Moderate[a]	3.7 mmHg [2.3 to 5]
Diastolic blood pressure - ≤ 6 hours	350 (14)	⊕⊕⊖⊖ Low[a,b]	-1.9 mmHg [-3.9 to 0.04]
Diastolic blood pressure - 7 to 12 hours	54 (5)	⊕⊕⊖⊖ Low[a,b]	-1.6 mmHg [-4.1 to 0.9]
Diastolic blood pressure - ≥ 13 hours	154 (4)	⊕⊕⊕⊖ Moderate[a]	2.4 mmHg [0.3 to 4.5]
Heart rate - ≤ 6 hours	495 (17)	⊕⊕⊕⊖ Moderate[a]	5.5 bpm [4.3 to 6.7]
Heart rate - 7 to 12 hours	144 (7)	⊕⊕⊕⊖ Moderate[a]	6.2 bpm [3 to 9.3]
Heart rate - ≥ 13 hours	244 (8)	⊕⊕⊕⊖ Moderate[a]	2.7 bpm [0.8 to 4.6]

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Unclear risk of selection bias and attrition bias in more than one study.
[b]95% confidence interval around the best effect estimate includes both negligible effect and appreciable benefit.

Summary of findings 2. Effect of medium-dose alcohol compared to placebo

Effect of medium-dose alcohol compared to placebo

Patient or population: adult participants
Setting: ambulatory
Intervention: medium-dose alcohol (15 to 30 g)
Comparison: placebo

Outcomes	Participants (RCTs)	Certainty of the evidence (GRADE)	Mean difference of medium-dose alcohol compared to placebo* (95% CI)
Systolic blood pressure - ≤ 6 hours	149 (10)	⊕⊕⊕⊖ Moderate[a]	-5.63 mmHg [-8.3 to -3]
Systolic blood pressure - 7 to 12 hours	54 (4)	⊕⊕⊖⊖ Low[a,b,c]	-3.2 mmHg [-8.4 to 2]
Systolic blood pressure - ≥ 13 hours	66 (5)	⊕⊕⊖⊖ Low[a,b]	0.6 mmHg [-3.9 to 5.2]
Diastolic blood pressure - ≤ 6 hours	149 (10)	⊕⊕⊕⊖ Moderate[c]	-4 mmHg [-6 to -2]
Diastolic blood pressure - 7 to 12 hours	54 (4)	⊕⊕⊖⊖ Low[a,b]	-1.2 mmHg [-4.3 to 1.9]
Diastolic blood pressure - ≥ 13 hours	66 (5)	⊕⊕⊕⊖ Moderate[b]	1.8 mmHg [-0.9 to 4.5]
Heart rate - ≤ 6 hours	181 (12)	⊕⊕⊕⊖ Moderate[c]	4.6 bpm [3.1 to 6.1]
Heart rate - 7 to 12 hours	54 (4)	⊕⊕⊖⊖ Low[a,b]	1.2 bpm [-1.9 to 4.3]
Heart rate - > 13 hours	36 (3)	⊕⊕⊖⊖ Low[a,b]	1.4 bpm [-2.1 to 4.9]

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Unclear risk of selection bias in more than one study.
[b]95% confidence interval around the effect estimate includes both appreciable benefit and appreciable harm.
[c]Unclear risk of selection bias and attrition bias in more than one study.

Summary of findings 3. Effect of low-dose alcohol compared to placebo

Effect of low-dose alcohol compared to placebo

Patient or population: adult participants
Setting: ambulatory
Intervention: low-dose alcohol (≥ 14 g)
Comparison: placebo

Outcomes	Participants (RCTs)	Certainty of the evidence (GRADE)	Mean difference of low-dose alcohol compared to placebo* (95% CI)
Systolic blood pressure - ≤ 6 hours	28 (2)	⊕⊕⊖⊖ Low[a,b]	-1.9 mmHg [-8.4 to 5.4]
Diastolic blood pressure - ≤ 6 hours	28 (2)	⊕⊕⊖⊖ Low[a,b]	-1.5 mmHg [-6.9 to 4]
Heart rate - ≤ 6 hours	28 (2)	⊕⊕⊕⊖ Moderate[a]	5.1 bpm [1.88 higher to 8.24]

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Unclear risk of selection bias.
[b]95% confidence interval around the best effect estimate includes both negligible effect and appreciable benefit.

BACKGROUND

Description of the condition

Hypertension, or elevated blood pressure, is commonly defined as resting systolic blood pressure (SBP) above 140 mmHg or resting diastolic blood pressure (DBP) above 90 mmHg - or both - assuming that the person is not taking any antihypertensive medication (Poulter 2015). It is one of the most common health conditions; hypertension has an increased prevalence with increasing age and affects up to 31% of the world's adult population (Mills 2016). Sustained hypertension is associated with increased risk of stroke, myocardial infarction, heart failure, renal failure, blindness, and cognitive impairment (Kannel 1972; WHO 2013). In 2015, approximately 10.7 million deaths around the world were estimated to be attributable to hypertension-related health complications (GBD 2015).

Hypertension can be genetic or may be due to environmental factors such as poor diet, obesity, tobacco use, excessive alcohol consumption, and sedentary lifestyle (Weber 2014; WHO 2013). A population-based study showed that the incidence of hypertension is higher in African descendants (36%) than in Caucasians (21%) (Willey 2014). Proper management of hypertension can lead to reduction in cardiovascular complications and mortality (Kostis 1997; SHEP 1991; Staessen 1999). Although pharmacological interventions can effectively reduce blood pressure, multiple studies have shown that a healthy lifestyle alone without any pharmacological interventions can greatly reduce the prevalence of hypertension (Appel 2003; Guitteau 2006). According to US guidelines for prevention, detection, evaluation, and management of high blood pressure, adults are advised to reduce weight and sodium intake, increase physical activity and potassium intake, cease smoking, and moderate alcohol intake to manage hypertension non-pharmacologically (Reboussin 2018).

Description of the intervention

Alcohol has been a part of almost every human culture for a very long time (McGovern 2009). According to the World Health Organization (WHO), around 2.3 billion people globally drink alcohol, and most of them are from the European region. On average, drinkers consume 32.8 grams of pure alcohol per day, and beer (34.3%) is the most consumed alcoholic beverage (WHO 2018). In the United States, 14 grams of pure alcohol is considered as one standard drink or one unit, and the maximum daily limit for men and women is four and three drinks, respectively (NIAAA 2017). Exceeding this limit increases the risk of cardiovascular, hepatic, and nervous system disorders (Bellentani 1997; Fuchs 2001; Gao 2011; Lieber 1998; McCullough 2011; Nutt 1999; Welch 2011). Also, multiple studies have found associations between consumption of alcoholic beverages and specific cancers (Kushi 2012; Seitz 2007). Abuse of alcohol resulted in approximately 3 million deaths worldwide and 132.6 million disability-adjusted life years (DALYs) in 2016 (WHO 2018).

Alcohol is water-soluble and can cross biological membranes by passive diffusion. It reaches equilibrium quickly if the body water content is higher. The presence of food in the stomach slows down alcohol absorption by retarding gastric emptying. Hence, it is recommended to not drink alcoholic beverages on an empty stomach. Alcohol is predominantly metabolised by the alcohol dehydrogenase (ADH) enzyme system and to a lesser extent by cytochrome P-450 2E1 in the liver. Alcohol is first metabolised to acetaldehyde and then is oxidised into acetyl coenzyme A (CoA) by aldehyde dehydrogenase (ALDH) (Cederbaum 2012). Although alcohol metabolism by the liver is well characterised, its metabolism in other parts of the body is not well defined. The enzyme catalase was found to be responsible for metabolising alcohol in the brain to produce acetaldehyde (Heit 2013). Acetaldehyde is highly reactive and has been associated with a wide range of physiological adverse effects (Zimatkin 2006).

Despite the potential negative effects of alcohol consumption, systematic reviews based on cohort studies show that light to moderate consumption of alcohol has a cardioprotective effect and may decrease mortality in adult men and women (Briasoulis 2012; Di Castelnuovo 2006; Plunk 2014; Taylor 2009).

How the intervention might work

The molecular mechanisms through which alcohol raises blood pressure are unclear. Alcohol can affect blood pressure through a variety of possible mechanisms. Previous research suggests that acute alcohol consumption affects the renin–angiotensin–aldosterone system (RAAS) by increasing plasma renin activity (Puddey 1985). The RAAS is responsible for maintaining the balance of fluid and electrolytes. An increase in plasma renin results in increased production of angiotensin I (AI), which is converted to angiotensin II (AII) by angiotensin-converting enzyme (ACE). The hormone AII is a potent vasoconstrictor that stimulates aldosterone and vasopressin secretion from the adrenal gland, promoting sodium and water retention (Schrier 1999). As a result, peripheral resistance and blood volume are increased, leading to elevated arterial blood.

Several clinical trials in humans and studies conducted in animal models have reported stimulation of the sympathetic nervous system and increased noradrenaline after consumption of alcohol (Barden 2013; Grassi 1989; Randin 1995; Russ 1991; Zhang 1989). When noradrenaline stimulates the adrenergic receptors located in the heart muscles, heart rate and blood pressure are increased.

Alcohol has been reported to diminish baroreceptor sensitivity, which is a key factor in regulating blood pressure (Abdel-Rahman 1985; Rupp 1996). Baroreceptors or stretch receptors are mechanoreceptors located on the arch of the aorta and the carotid sinus. They can detect changes in blood pressure and can maintain blood pressure by controlling heart rate, contractility, and peripheral resistance. Acute administration of alcohol stimulates the release of histamine and endorphin, which interferes with baroreflex sensitivity (Carretta 1988).

Another possible mechanism is the increase in plasma cortisol levels following heavy alcohol consumption (Jenkins 1968). Several studies have suggested a role for cortisol in alcohol-induced hypertension (Husain 2014; Potter 1986). Cortisol is a type of steroid hormone, and the presence of excess cortisol has been associated with elevated blood pressure in normotensive individuals (Whitworth 1984; Whitworth 2005).

Alcohol can affect drinkers differently based on their age, sex, ethnicity, family history, and liver condition (Cederbaum 2012; Chen 1999; Gentry 2000; Thomasson 1995). Previous studies reported that women are affected more than men after drinking the same amount of alcohol because of their lower body weight

and higher body fat. The blood alcohol concentration (BAC) rises faster in women because they have a smaller volume of distribution (Kwo 1998). In contrast, women eliminate alcohol from the body a little faster than men (Thomasson 2000). Different genetic variants of ADH and ALDH enzymes have been found to show strikingly different rates of alcohol metabolism among different races (Chen 1999; Peng 2014; Agarwal 1981).

Why it is important to do this review

Several systematic reviews based on cohort studies have concluded that alcohol intake has a considerable effect on blood pressure and on risk of hypertension (Chen 2008; Worm 2013). It has also been shown that heavy alcohol consumption causes hypertension and leads to left ventricular dysfunction and dilated cardiomyopathy. On the other hand, abundant epidemiological and clinical evidence shows that light to moderate drinking is associated with reduced risk of coronary heart disease (CHD), incidence of stroke, and total mortality among middle-aged and elderly men and women (Abramson 2001 ; Briasoulis 2012; Di Castelnuovo 2006; Djoussé 2007 ; Jaubert 2014; Plunk 2014; Taylor 2009).

All these conclusions are based on findings of observational studies. Several RCTs have reported the magnitude of effect of alcohol on blood pressure, but because those trials are small, their findings are not sufficient to justify a strong conclusion. In 2005, McFadden and colleagues conducted a systematic review of RCTs, which investigated the haemodynamic effects of daily consumption of alcohol (McFadden 2005). Based on nine RCTs in which participants consumed alcohol repeatedly over days, these review authors reported that alcohol increases SBP by 2.7 mmHg and DBP by 1.4 mmHg. However, they excluded studies for which the duration of BP observation was less than 24 hours and articles published in non-English languages. We believe that inclusion of those studies will provide useful information about the dose-related magnitude and time-course effect of alcohol on blood pressure in people with both normal and elevated blood pressure.

OBJECTIVES

Primary objectives

To determine short-term dose-related effects of alcohol versus placebo on systolic blood pressure and diastolic blood pressure in healthy and hypertensive adults over 18 years of age.

Secondary objective

To determine short-term dose-related effects of alcohol versus placebo on heart rate in healthy and hypertensive adults over 18 years of age.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) that compared alcohol to placebo or similar tasting non-alcoholic beverages were included in this systematic review.

Types of participants

We included adult (≥ 18) participants of both sexes without any restriction on their health condition.

Types of interventions

We included any type of alcoholic beverage as the intervention arm. The dose of alcohol had to be reported by study authors for inclusion in the systematic review. Because there are no published standards for differentiating between low and medium doses of alcohol, we chose the alcohol content in one standard drink as the threshold between low dose and medium dose. Because the alcohol content in one standard drink varies among different countries (ranging from 8 g to 14 g), we chose the Canadian standard for an alcoholic beverage, which is 14 g of pure alcohol (CCSA). Accordingly, we considered up to 14 g of alcohol as a low dose of alcohol. To differentiate between medium and high doses, the Canadian Centre on Substance Use and Addiction (CCSA) identifies less than 30 g of alcohol for men and less than 20 g of alcohol for women as the threshold for low risk of alcohol intake (CCSA). Thus, in our review, we used up to 30 g alcohol intake for men and up to 20 g alcohol intake for women as a moderate dose, and above this limit as a high dose. In studies where sex-specific results were not provided, we categorised dose based on the dominating sex in terms of study participation. In conclusion, we categorised doses of alcohol as follows.

- Low dose (≤ 14 g of alcohol/≤ 1 standard drink).
- Medium dose (> 14 g and ≤ 30 g of alcohol for men and > 14 g and ≤ 20 g of alcohol for women).
- High dose (> 30 g of alcohol for men and > 20 g of alcohol for women).

Types of outcome measures

Primary outcomes

- Change in resting seated systolic and diastolic blood pressures at three different time periods after alcohol intake: early (up to six hours); intermediate (7 to 12 hours); and late (≥ 13 hours)

Secondary outcomes

- Change in resting heart rate at the same time periods as blood pressure outcomes above

Additional outcomes

- Change in resting mean arterial pressure (MAP) at the same time periods as blood pressure outcomes above

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist searched the following databases without language, publication year, or publication status restrictions.

- Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 14 March 2019).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 2), in the Cochrane Library, via the Cochrane Register of Studies (CRS-Web) (searched 14 March 2019).
- MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 14 March 2019).
- Embase Ovid (from 1974 onwards) (searched 14 March 2019).

- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 14 March 2019).
- World Health Organization International Clinical Trials Registry Platform (www.who.it.trialsearch) (searched 14 March 2019).

The Information Specialist modelled subject strategies for databases on the search strategy designed for MEDLINE. When appropriate, these were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.c. (Higgins 2011)). We present search strategies for major databases in Appendix 1.

Searching other resources

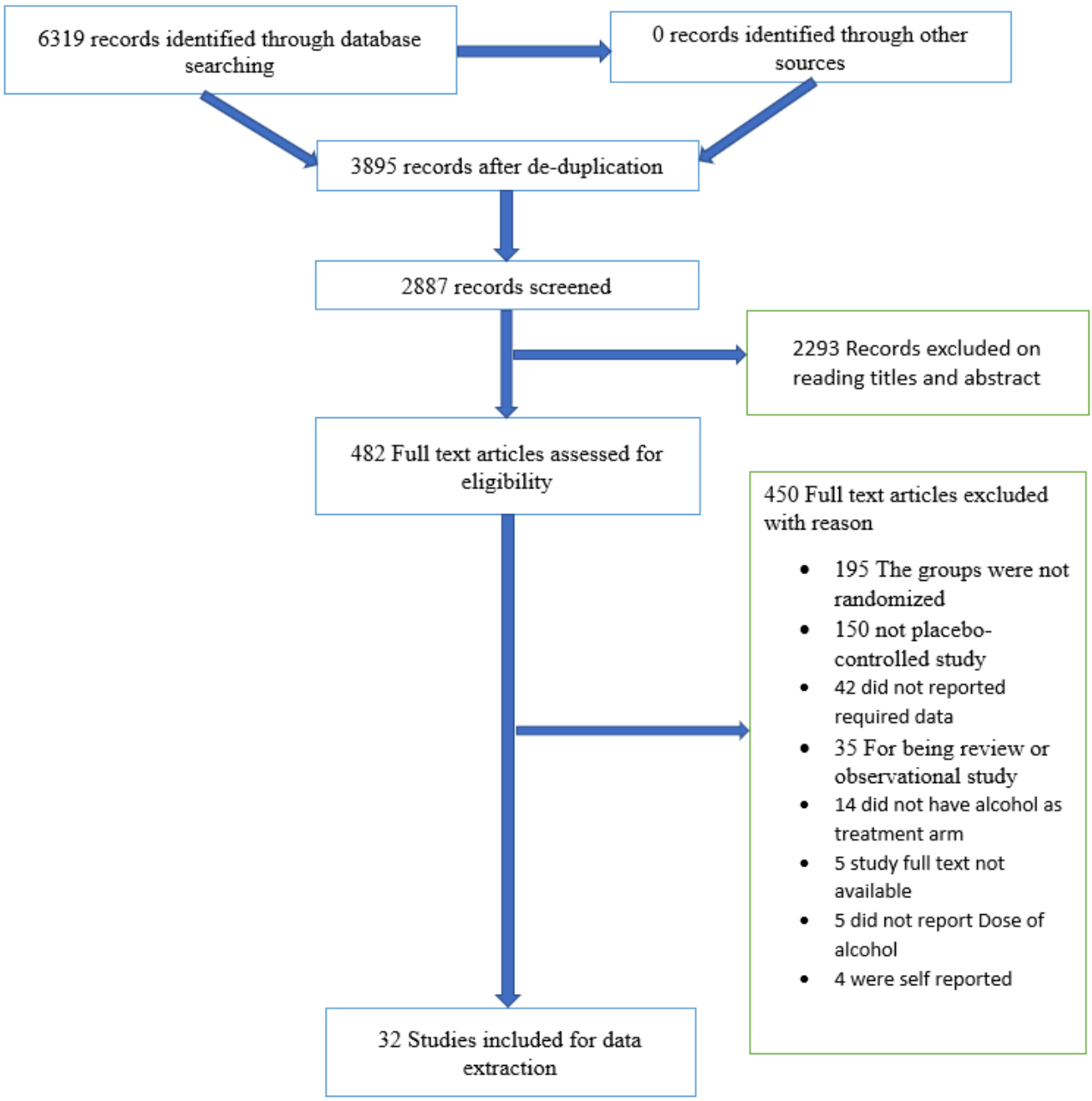
- The Cochrane Hypertension Information Specialist searched the Hypertension Specialised Register segment (which includes searches of MEDLINE, Embase, and Epistemonikos for systematic reviews) to retrieve existing reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Specialised Register also includes searches of CAB Abstracts & Global Health, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), ProQuest Dissertations & Theses, and Web of Science for controlled trials
- We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials
- When necessary, we contacted authors of key papers and abstracts to request additional information about their trials

Data collection and analysis

Selection of studies

We (ST and CT) independently screened the citations found through the database search using Covidence software (Covidence). We excluded articles if the citation seemed completely irrelevant or was identified as a review or observational study after the title and abstract were read. For remaining studies, we (ST and CT) retrieved full-text articles for further assessment. Any disagreements regarding inclusion or exclusion of studies were resolved by discussion between review authors. The reason for exclusion was documented for each citation at the full-text level. We also checked the list of references in the included studies and articles that cited the included studies in Google Scholar to identify relevant articles. We reported the flow of citation in Figure 1.

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (ST and CT) performed data extraction independently using a standard data collection form, followed by a cross-check. In cases of disagreement, the third review authors (JMW) became involved to resolve the disagreement. When necessary, we contacted the authors of studies for information about unclear study design. We recorded study design, type of masking, randomisation and allocation concealment methods, details of intervention and comparator, duration of intervention, baseline characteristics of participants, whether food was consumed before or during the intervention, numbers of participants included in the final analysis, outcomes and results, method and position of BP measurement, declaration of conflict of interest, funding source, and protocol registration number. All extracted data were entered and double-checked in RevMan 5.3 software (Review Manager (RevMan)).

Assessment of risk of bias in included studies

We (ST and CT) assessed the risk of bias of included studies independently using the Cochrane risk of bias tool (version 1) according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* for the following domains (Higgins 2011).

- Sequence generation (selection bias).
- Allocation sequence concealment (selection bias).
- Blinding of participants (performance bias).

- Blinding of outcome assessors (detection bias).
- Incomplete outcome data (attrition bias).
- Selective outcome reporting (reporting bias).
- Other potential sources of bias (i.e. conflict of interest, funding source, registration of the study protocol).

We assessed selective reporting bias for each of the outcomes separately. For the other domains, we grouped outcomes together and provided only one judgement. We contacted study authors for missing or unclear information required for the risk of bias assessment and then reassessed the domains once the information was available.

Measures of treatment effect

All outcomes of interest in the review (BP and HR) produced continuous data. We calculated and reported mean difference (MD), with corresponding 95% confidence interval (95% CI).

Unit of analysis issues

Most of the studies included in the review had a cross-over design. The carry-over effect in a cross-over trial can confound the effects of subsequent treatment. We recorded the washout period of each included study reported by study authors to decide if there was risk of a carry-over effect. If it was appropriate to combine cross-over trials with other trials, we used the recommended generic inverse variance approach of meta-analysis. We tested the effect of cross-over trials through sensitivity analysis by excluding them from the meta-analysis to check if the effect estimate changed significantly.

For multi-arm trials, if a study reported more than one intervention arm, we identified the relevant intervention arm and included that in the review. If studies reported more than one placebo group, we combined them into a single group when appropriate, using the formulae for combining groups reported in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We followed the same formulae for combining groups if a study reported two different types of alcoholic beverages containing the same amount of alcohol.

Dealing with missing data

General missing data

We contacted the study authors for missing or unclear information relevant to the review using contact information provided in their respective articles. If the dose of a study was not reported in the article and the study author did not respond to our request, we excluded that study.

Missing statistics

If a standard error (SE) was given instead of a standard deviation (SD), we used the formula SD = SE × square root of n (number of participants) to calculate the SD.

We also calculated SD if 95% CI, P value, or t value was reported in the included studies, according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we were not able to get SD from the study authors or calculate SD from the values mentioned above, we imputed SD using the following hierarchy (listed from highest to lowest) (Musini 2014).

- SD of change in blood pressure measured in a different position (e.g. lying down) than that of the blood pressure data used.
- SD of blood pressure at the end of treatment.
- SD of blood pressure at the end of treatment measured in a different position (e.g. lying down) than that of the blood pressure data used.
- SD of blood pressure at baseline (unless this measure was used as an entry criterion).
- Mean SD of change in blood pressure from other studies that studied the effects of alcohol.

Assessment of heterogeneity

We conducted a standard Chi^2 test through Review Manager Software 5.3 to test for heterogeneity (Review Manager (RevMan)). A P value of 0.1 or less was considered to show statistically significant heterogeneity. The I^2 statistic was used to interpret the level of heterogeneity (Higgins 2011). For the purposes of this review, if I^2 was greater than 50%, it was considered to show a substantial level of heterogeneity. Furthermore, we visually inspected the forest plot to check whether there were any non-overlapping confidence intervals indicating heterogeneity. Last, we attempted to explore the reason for heterogeneity by looking for clinical and methodological differences between trials.

Assessment of reporting biases

We used funnel plots if there were more than 10 studies that contributed to a meta-analysis to detect the extent of risk of reporting bias based on symmetry of the plot (Higgins 2011). We visually inspected the funnel plots. If the residual scatter plot resembles a symmetrical inverted funnel, we considered publication bias to be unlikely. Positive results are more likely to be published than negative results, which leads to potential publication bias. However, publication bias does not necessarily lead to asymmetry in funnel plots. Asymmetry in the funnel plot can also be due to inflated effects in smaller studies resulting from poor study design, heterogeneity, sampling variation, or chance. Therefore, we performed sensitivity analyses and searched for unpublished studies as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

Data synthesis

We used Cochrane review manager software for all data analyses (Review Manager (RevMan)). We conducted meta-analysis for the three dose groups (low dose, medium dose, and high dose of alcohol) separately. We considered statistical, clinical, and methodological heterogeneity between study populations and proceeded with the meta-analysis if only we considered interventions, comparisons, and outcome measures similar enough to pool. When trials compared more than one dose of alcohol, we handled each comparison separately. Because all of our outcomes of interest provided continuous data, we used the inverse variance approach and a fixed-effect model to combine effect sizes across studies.

Subgroup analysis and investigation of heterogeneity

We planned on performing subgroup analysis based on the following.

- Normotensive participants (defined as SBP < 140 mmHg and DBP < 90 mmHg) versus hypertensive participants (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg).
- Sex of participants.

It is recommended that there should be at least 10 studies reporting each of the subgroups in question (Deeks 2011). Among the 34 included studies, only four studies included hypertensive participants. So, it was not possible to conduct a subgroup analysis based on blood pressure. For the planned subgroup analysis based on sex, no study reported male and female participant data separately.

Sensitivity analysis

We performed the following sensitivity analyses.

- We checked if blinding of participants and outcome assessors affected the effect estimate of BP and HR (blinded studies versus unblinded studies).
- We checked the difference between effect estimates of outcomes given by the fixed-effect model and the random-effects model by conducting sensitivity analysis. We did this only when heterogeneity was substantial.

Summary of findings and assessment of the certainty of evidence

We used the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) to assess the certainty of a body of evidence as high, moderate, low, or very low and provided review authors' comments to support our judgements as outlined in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* ((Guyatt 2011 Higgins 2011). We included the outcomes SBP, DBP, and HR for each comparison. Both review authors (ST and CT) rated the certainty of evidence independently by examining risk of bias, indirectness, inconsistency, imprecision, and publication bias.

To assess risk of bias across studies, we rated the evidence as having no limitations, serious limitations, or very serious limitations while taking into account the extent that each trial contributes towards the magnitude of effect (weight) as based on its study sample size and mean difference.

We used GRADEpro software to construct a 'Summary of findings' table to compare outcomes including change in SBP and DBP and HR (GRADEpro 2014). In addition, we included illustrative risks to present findings for the most important outcome (change in systolic blood pressure).

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) (Guyatt 2011) to assess the certainty of the body evidence as high, moderate, low or very low and provide review authors' comments to support our judgements as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* chapter 12 (Higgins 2011). We included the outcomes SBP, DBP and HR for each comparison. Both reviewers (ST and CT) rated the certainty of evidence independently by examining risk of bias, indirectness, inconsistency, imprecision, and publication bias.

To assess the risk of bias across studies, we rated the evidence as having no limitations, serious limitations, or very serious limitations while taking into account the extent that each trial contributes towards the magnitude of effect (weight) as based on their study sample size and mean difference.

We used GRADEpro software (GRADEpro 2014) to construct a 'Summary of findings' table to compare outcomes including change in SBP and DBP and HR. In addition, we also included illustrative risks to present findings for the most important outcome (change in systolic blood pressure)

RESULTS

Description of studies

Results of the search

The search was conducted up to March 2019 and resulted in 6869 citations. After de-duplication and screening of titles and abstracts, we were left with 482 citations for further assessment. We retrieved full-text articles for those citations and included 32 studies (Figure 1).

Included studies

Refer to Characteristics of included studies and Table 1 for further details regarding these studies.

Of the 32 included RCTs involving 767 participants, 26 trials used a cross-over design and six used a parallel-group design. Three studies were single-blind, 12 were double-blind, and 17 were open-label studies. Most study participants were male (N = 642). The age of participants ranged from 18 to 96 years, and mean participant age was 33 years. Stott 1991 included relatively old participants (mean age 81, range 70 to 96 years) compared to the other studies. Only 14 out of 34 studies reported the mean body weight of participants. The mean body weight from those 14 studies was 78 kg. Most studies included healthy participants with normal blood pressure. Some studies included small numbers of participants with essential hypertension (10%) (Foppa 2002 Hering 2011; Kawano 1992; Kawano 2000; Kojima 1993), type 1 diabetes (2.2%) (Cheyne 2004), coronary heart disease (6.3%) (Karatzi 2005 Rossinen 1997 Williams 2004) and regular user of methylenedioxy methamphetamine (MDMA) (2%) (Dumont 2010).

Different types of alcoholic beverages including red wine, white wine, beer, and vodka were used among 32 studies. Out of 32 studies, 23 used non-alcoholic beverages including juice as placebo (Bau 2005; Bau 2011 Buckman 2015; Cheyne 2004; Dai 2002; Dumont 2010; Fazio 2004; Foppa 2002; Hering 2011; Kawano 1992; Kawano 2000; Koenig 1997; Kojima 1993; Maufrais 2017; Maule 1993; Narkiewicz 2000; Rosito 1999; Rossinen 1997; Stott 1987; Stott 1991; Van De Borne 1997; Williams 2004; Zeichner 1985); seven studies used de-alcoholised wine as placebo (Agewall 2000; Barden 2013; Karatzi 2005; Karatzi 2013; Mahmud 2002; Nishiwaki 2017; Potter 1986); and two studies did not mention the type of control they used for alcohol (Chen 1986; Fantin 2016). The dose of alcohol ranged between 0.35 mg/kg and 1.3 g/kg, and alcohol was consumed over five minutes and over one hour and 30 minutes. It is important to note that the dose of alcohol was comparatively higher (≥ 60 g or ≥ 1 g/kg) in nine studies (Bau 2005; Buckman 2015; Hering 2011; Narkiewicz 2000; Rosito 1999; Rossinen 1997; Stott 1987; Van De Borne 1997; Zeichner 1985).

Excluded studies

We excluded 450 trials after reviewing the full-text articles, and we recorded the reasons for exclusion (see table Characteristics of excluded studies table).

Risk of bias in included studies

Refer to Figure 2 and Figure 3 for the overall 'Risk of bias' assessment.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

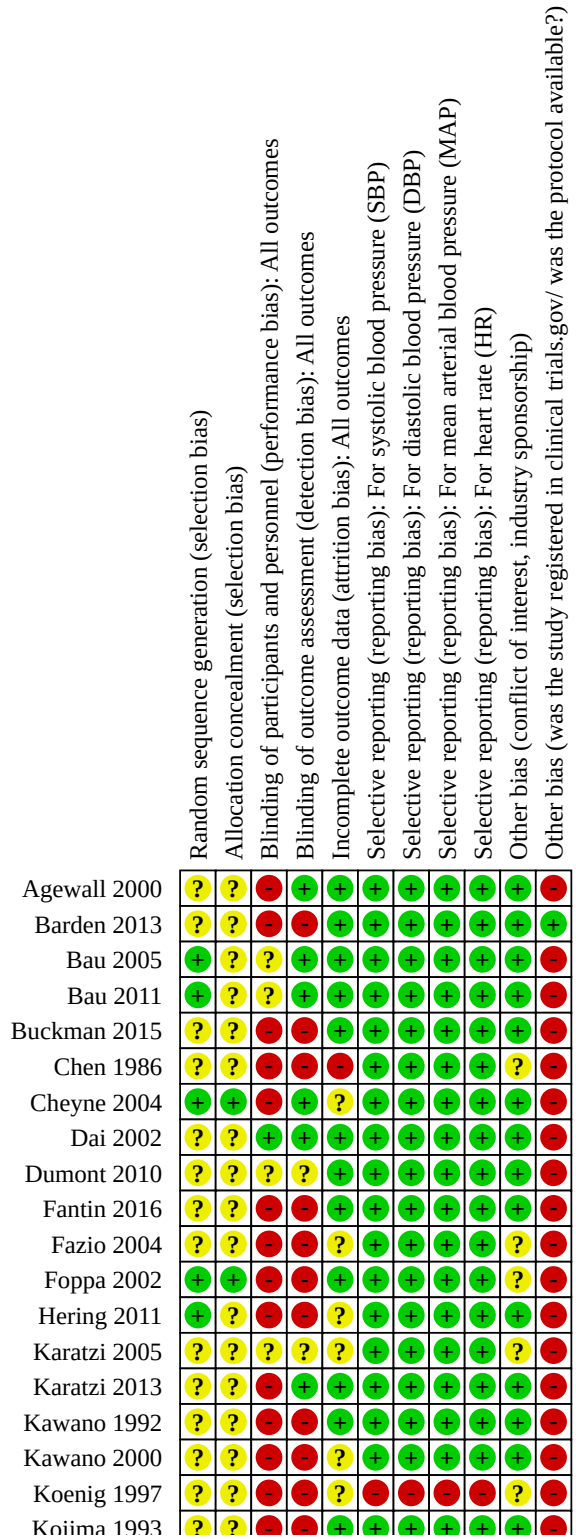


Figure 2. (Continued)

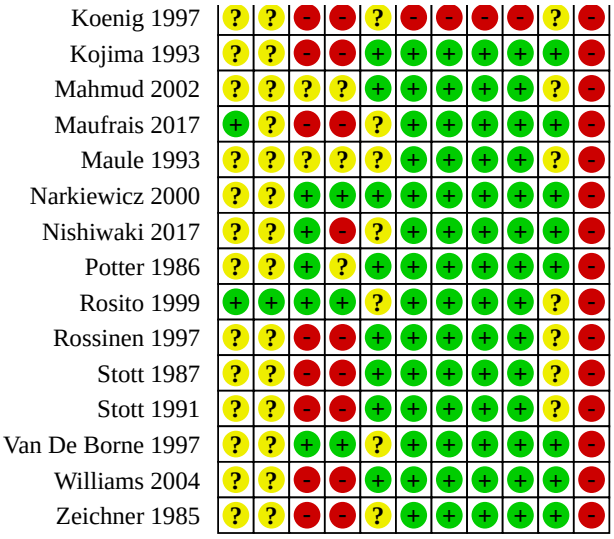
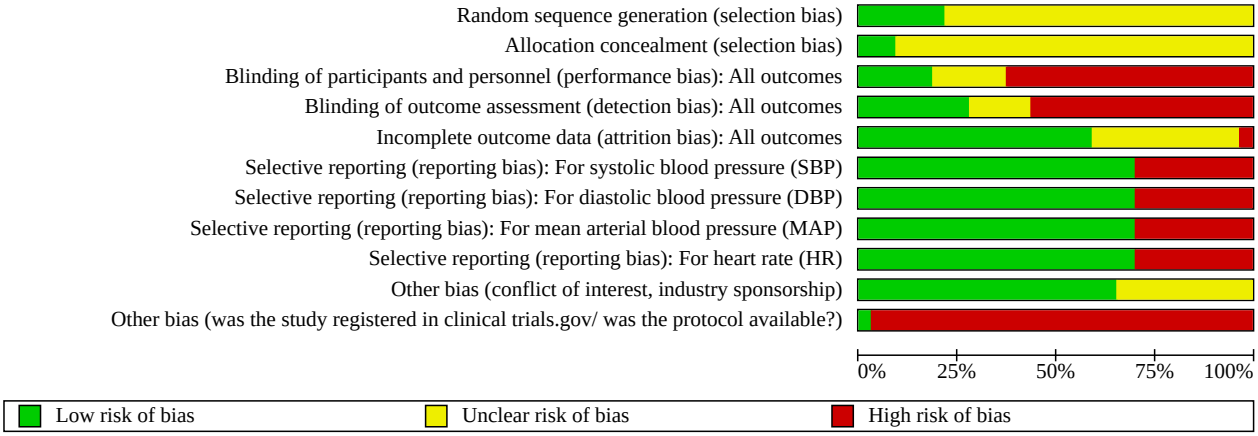


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



We (ST and CT) independently assessed risk of bias by following the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the risk of bias based on 11 domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) for systolic blood pressure (SBP), selective reporting (reporting bias) for diastolic blood pressure (DBP), selective reporting (reporting bias) for mean arterial blood pressure (MAP), selective reporting (reporting bias) for heart rate (HR), other bias (conflict of interest, industry sponsorship), and other bias (was the study registered in clinical trials.gov and was the protocol available). We classified each domain as being at low, high, or uncertain risk of bias.

In the case of disagreement, a third party (JMW) was involved to discuss and resolve the disagreement. In the case of uncertain information regarding the method of RCT, we contacted study authors via email to request clarification. Refer to Table 2 for further details regarding reasons and responses.

Allocation

We (ST and CT) assessed selection bias based on two categories: random sequence generation and allocation concealment.

Random sequence generation

For random sequence generation, we classified 22 included studies as having uncertain risk of bias (Agewall 2000; Chen 1986; Dumont 2010; Fantin 2016; Fazio 2004; Karatzi 2005; Karatzi 2013; Kawano 1992; Kawano 2000; Koenig 1997; Kojima 1993; Mahmud 2002; Maule 1993; Narkiewicz 2000; Nishiwaki 2017; Potter 1986; Rossinen 1997; Stott 1987; Stott 1991; Van De Borne 1997; Williams 2004; Zeichner 1985). Even though these studies reported that participants were randomised to receive alcohol or placebo, the

method of randomisation was not mentioned. Although three studies did not report the method of randomisation (Barden 2013; Buckman 2015; Dai 2002), their reported baseline characteristics were well matched. We classified them as having uncertain risk of bias. The remaining seven studies reported the method of randomisation used, hence we classified them as having low risk of bias. Random seed generation was used in Bau 2005 and Bau 2011 computer-generated random selection of 4 × 4 Latin squares was used in Cheyne 2004 a third person unaware of research objectives or protocol prepared sealed randomised envelops in blocks of eight in Foppa 2002; a randomised computer-generated number table was used in Hering 2011; a random sequence generator was used in Maufrais 2017; and a random number allocator was used in Rosito 1999. It is important to note that information regarding to the method of randomisation used in Foppa 2002 and Rosito 1999 was provided by the study author via email. Refer to Table 2 for further details.

For allocation concealment, we classified 28 included studies as having uncertain risk of bias because the method of allocation concealment was not reported (Agewall 2000; Bau 2005; Bau 2011; Buckman 2015; Chen 1986; Dai 2002; Dumont 2010; Fantin 2016; Fazio 2004; Hering 2011; Karatzi 2005; Karatzi 2013; Kawano 1992; Kawano 2000; Koenig 1997; Kojima 1993; Mahmud 2002; Maufrais 2017; Maule 1993; Narkiewicz 2000; Nishiwaki 2017; Potter 1986; Rossinen 1997; Stott 1987; Stott 1991; Van De Borne 1997; Williams 2004; Zeichner 1985). We classified the remaining four studies as having low risk of bias. In Barden 2013, treatment allocation was performed by a statistician who was not involved in the trial. Opaque sealed randomised envelopes were used in Cheyne 2004 and Foppa 2002, and random number allocator was used in Rosito 1999. It is important to note that information regarding the method of allocation concealment used in Foppa 2002 and Rosito 1999 was provided by the study author via email. We also contacted Hering 2011, but the study author did not explicitly mention in the email the method of allocation concealment used. Thus, we classified this study as having uncertain risk of bias. Refer to Table 2 for further details.

Blinding

In the case of performance bias, we classified six studies as having low risk of bias, 19 studies as having high risk of bias, and seven studies as having unclear risk of bias.

We classified six studies as having low risk of performance bias (Dai 2002; Narkiewicz 2000; Nishiwaki 2017; Potter 1986; Rosito 1999; Van De Borne 1997). Nishiwaki 2017 was a single-blinded study. In this study, all test drinks were poured into paper cups to achieve blinding of participants. We contacted the author of Rosito 1999 to request additional information regarding the method of blinding used. The study author explained the blinding method in detail in an email, so we classified this study as having low risk of bias.

We classified 19 studies as having high risk of performance bias. Of 19 studies, 17 were open-label (Barden 2013; Buckman 2015; Chen 1986; Fantin 2016; Fazio 2004; Foppa 2002; Hering 2011; Kawano 1992; Kawano 2000; Koenig 1997; Kojima 1993; Maufrais 2017; Rossinen 1997; Stott 1987; Stott 1991; Williams 2004; Zeichner 1985), hence these studies were not blinded for participants nor for personnel. It is important to note that 2 out of 19 studies were single-blinded (Agewall 2000; Karatzi 2013). Personnel were blinded instead of participants in Karatzi 2013, and neither personnel nor participants were blinded in Agewall 2000, so we assessed these studies as having high risk of bias.

We classified seven studies as having unclear risk of performance bias (Bau 2005; Bau 2011; Cheyne 2004; Dumont 2010; Karatzi 2005; Mahmud 2002; Maule 1993). Bau 2005 and Bau 2011 mentioned only that investigators and volunteers were blinded to the content of the drink but did not mention the method of blinding used in these studies. Karatzi 2005 mentioned the method of blinding of participants, but it is not clear whether involved personnel were blinded as well. The method of blinding of participants and personnel was not mentioned in Dumont 2010, Mahmud 2002, and Maule 1993. In Cheyne 2004, participants were blinded to the content of the drink, but some reported that they were able to detect the alcohol by taste at the end of the study. Hence, we classified this study as having high risk of bias.

In the case of detection bias, we classified nine studies as having low risk of performance bias (Agewall 2000; Bau 2005; Bau 2011; Cheyne 2004; Dai 2002; Karatzi 2013; Narkiewicz 2000; Rosito 1999; Van De Borne 1997). All studies included an independent individual who was blinded to control and test groups to evaluate and analyse the data. We classified 17 studies as having high risk of bias because they were described as open-label studies, and because the outcome assessor was not blinded (Barden 2013; Buckman 2015; Chen 1986; Fantin 2016; Fazio 2004; Foppa 2002; Hering 2011; Kawano 1992; Kawano 2000; Koenig 1997; Kojima 1993; Maufrais 2017; Rossinen 1997; Stott 1987; Stott 1991; Williams 2004; Zeichner 1985). One study - Nishiwaki 2017 (a single-blinded study) - ensured participant blinding but not blinding of outcome assessors. We classified five studies as having uncertain risk of detection bias. Karatzi 2005, Mahmud 2002, Maule 1993, and Potter 1986 did not mention the method of blinding of outcome assessors. Even though Dumont 2010 mentioned blinding of outcome assessors, it is not clear whether blinding of outcome assessment was maintained in the case of blood pressure and heart rate measurements.

Incomplete outcome data

We classified 18 studies as having low risk of attrition bias (Agewall 2000; Barden 2013; Bau 2005; Bau 2011; Dai 2002; Dumont 2010; Fantin 2016; Foppa 2002; Karatzi 2013; Kawano 1992; Kojima 1993; Mahmud 2002; Narkiewicz 2000; Potter 1986; Rossinen 1997; Stott 1987; Stott 1991; Williams 2004). Dumont 2010, Karatzi 2013, Kawano 1992, and Williams 2004 reported reasons for participant withdrawal and excluded their data from the final analysis. Data were balanced across groups, hence missing data did not affect the final results.

We classified one study as having high risk of bias. Chen 1986 reported that two participants in the alcohol group dropped out of the study for unknown reasons, so data analyses were based on eight participants in the alcohol group and on 10 participants in the control group. Because the reasons behind withdrawal were not mentioned in this study, we considered this study to have high risk of bias.

We classified 13 studies as having uncertain risk of attrition bias because study authors did not explicitly mention whether all participants were included in the final analysis (Buckman 2015; Cheyne 2004; Fazio 2004; Hering 2011; Karatzi 2005; Kawano 2000; Koenig 1997; Maufrais 2017; Maule 1993; Nishiwaki 2017; Rosito 1999; Van De Borne 1997; Zeichner 1985).

Selective reporting

We (ST and CT) assessed reporting bias based on four categories: selective reporting of systolic blood pressure (SBP), selective reporting of diastolic blood pressure (DBP), selective reporting of mean arterial blood pressure (MAP), and selective reporting of heart rate (HR).

In the case of selective reporting of systolic blood pressure (SBP), we classified 25 studies as having low risk of bias because they recorded and reported SBP in the Results section or in the Figure (Barden 2013; Bau 2005; Buckman 2015; Chen 1986; Cheyne 2004; Dai 2002; Fantin 2016; Foppa 2002; Hering 2011; Karatzi 2005; Kawano 1992; Kawano 2000; Koenig 1997; Kojima 1993; Mahmud 2002; Maule 1993; Narkiewicz 2000; Nishiwaki 2017; Potter 1986; Rosito 1999; Rossinen 1997; Stott 1987; Stott 1991; Williams 2004; Zeichner 1985). We classified seven studies as having high risk of bias (Agewall 2000; Bau 2011; Dumont 2010; Fazio 2004; Karatzi 2013; Maufrais 2017; Van De Borne 1997). Agewall 2000 measured blood pressure upon arrival of participants and did not measure blood pressure after the intervention. The aim of Bau 2011 was to determine the effects of alcohol on heart rate variability, so SBP was not measured in this study. Dumont 2010 measured blood pressure during the study period, but study authors did not provide the before and after measurement of SBP. They mentioned only that change in blood pressure was not significant. The aim of Fazio 2004 was to determine the effects of alcohol on blood flow volume and velocity. Blood pressure was also measured but was not reported. Study authors mentioned only that acute ethanol administration caused a transitory increase in BP at 20 minutes. Karatzi 2013 Maufrais 2017 and Van De Borne 1997 measured blood pressure before and after treatment but did not report these measurements.

In the case of selective reporting of diastolic blood pressure (DBP), we classified 23 studies as having low risk of bias because they measured and reported DBP in the Results section or in the figure (Barden 2013; Bau 2005; Chen 1986; Cheyne 2004; Dai 2002; Fantin 2016; Foppa 2002; Hering 2011; Karatzi 2005; Kawano 1992; Kawano 2000; Koenig 1997; Kojima 1993; Mahmud 2002; Maule 1993; Narkiewicz 2000; Nishiwaki 2017; Potter 1986; Rosito 1999; Stott 1987; Stott 1991; Williams 2004; Zeichner 1985). We classified nine studies as having high risk of bias (Agewall 2000; Bau 2011; Buckman 2015; Dumont 2010; Fazio 2004; Karatzi 2013; Maufrais 2017; Rossinen 1997; Van De Borne 1997). Agewall 2000 measured blood pressure upon participants' arrival and did not measure blood pressure after the intervention. The aim of Bau 2011 was to determine the effects of alcohol on heart rate variability, so study authors did not measure and report DBP. For Buckman 2015, blood pressure was recorded beat to beat continuously, but DBP was not reported. Dumont 2010 measured blood pressure during the RCT, but study authors did not provide the before and after measurement of DBP. They mentioned that changes in blood pressure were not significant. The aim of Fazio 2004 was to determine effects of alcohol on blood flow volume and velocity. Blood pressure was also measured but was not reported. Study authors mentioned that acute ethanol administration caused transitory increase in BP at 20 minutes. Rossinen 1997 measured blood pressure but selectively reported only SBP instead of reporting both SBP and DBP. Karatzi 2013 Maufrais 2017 and Van De Borne 1997 measured blood pressure before and after treatment but did not report these measurements.

For selective reporting of mean arterial blood pressure (MAP), we classified 11 studies as having low risk of bias because MAP was measured and reported (Buckman 2015; Dumont 2010; Fazio 2004; Foppa 2002; Karatzi 2005; Karatzi 2013; Kojima 1993; Maufrais 2017; Maule 1993; Narkiewicz 2000; Van De Borne 1997). We classified 21 studies as having high risk of bias because they did not report MAP (Agewall 2000; Barden 2013; Bau 2005; Bau 2011; Chen 1986; Cheyne 2004; Dai 2002; Fantin 2016; Hering 2011; Kawano 1992; Kawano 2000; Koenig 1997; Mahmud 2002; Nishiwaki 2017; Potter 1986; Rosito 1999; Rossinen 1997; Stott 1987; Stott 1991; Williams 2004; Zeichner 1985).

For selective reporting for heart rate (HR), we classified only Koenig 1997 as having high risk of bias because heart rate was not reported. We classified the remaining 33 studies as having low risk of bias because heart rate was measured and reported.

Other potential sources of bias

We divided other potential sources of bias into two main categories: conflict of interest/industry sponsorship and registration with clinical trials.gov.

In the case of assessing conflicts of interest and industry sponsorship, we classified 21 studies as having low risk of bias because they reported industry sponsorship and had no conflicts of interest (Agewall 2000; Barden 2013; Bau 2005; Bau 2011; Buckman 2015; Cheyne 2004; Dai 2002; Dumont 2010; Fantin 2016; Hering 2011; Karatzi 2013; Kawano 1992; Kawano 2000; Kojima 1993; Maufrais 2017; Narkiewicz 2000; Nishiwaki 2017; Potter 1986; Van De Borne 1997; Williams 2004; Zeichner 1985). We classified 11 studies as having uncertain risk of bias because the funding source or conflicts of interest were not reported (Chen 1986; Fazio 2004; Foppa 2002; Karatzi 2005; Koenig 1997; Mahmud 2002; Maule 1993; Rosito 1999; Rossinen 1997; Stott 1987; Stott 1991).

In the case of registration at clinical trials.gov, we considered only one study to have low risk of bias (Barden 2013). The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR). We classified the remaining studies as having high risk of bias because the protocol was not registered and the study identifier was not reported. Therefore, it is difficult to determine a priori selection of primary and secondary outcome measures for the included studies.

Publication bias

We did not identify enough studies to construct a funnel plot for the outcomes under low doses of alcohol. We interpreted only funnel plots that were constructed based on studies reporting outcomes under medium dose and high dose of alcohol versus placebo comparisons.

We created a funnel plot using the mean difference (MD) from studies reporting effects of medium doses and high doses of alcohol on SBP, DBP, MAP, and HR against standard error (SE) of the MD to check for the existence of publication bias. Visual inspection of funnel plots shows that the effect estimate is equally distributed around the mean in Figure 4, Figure 5, Figure 6. Figure 7, and Figure 8. In Figure 9, Figure 10, and Figure 11, we observed slight asymmetry in the funnel plot that was probably due to heterogeneity rather than to publication bias. We noted some overlap of data points in some funnel plots, indicating that some of the included studies were of similar size. According to Chapter 10

of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), a funnel plot asymmetry test should not be used if all studies are of similar size. In this review, most of the included studies are of similar size.

Figure 4. Funnel plot of comparison: 2 Medium-dose alcohol vs placebo, outcome: 2.4 Heart rate.

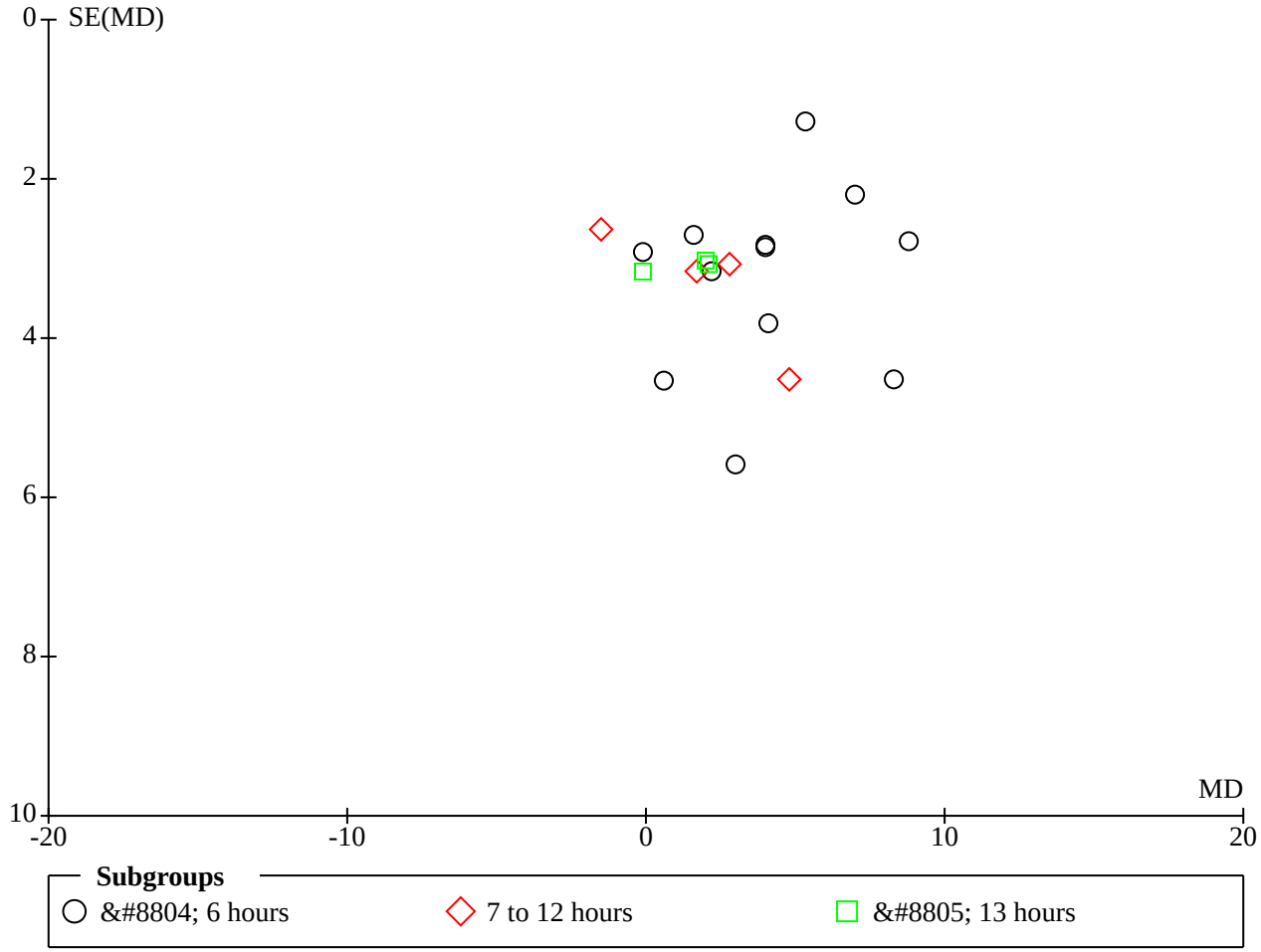


Figure 5. Funnel plot of comparison: 3 High-dose alcohol vs placebo, outcome: 3.1 Systolic blood pressure.

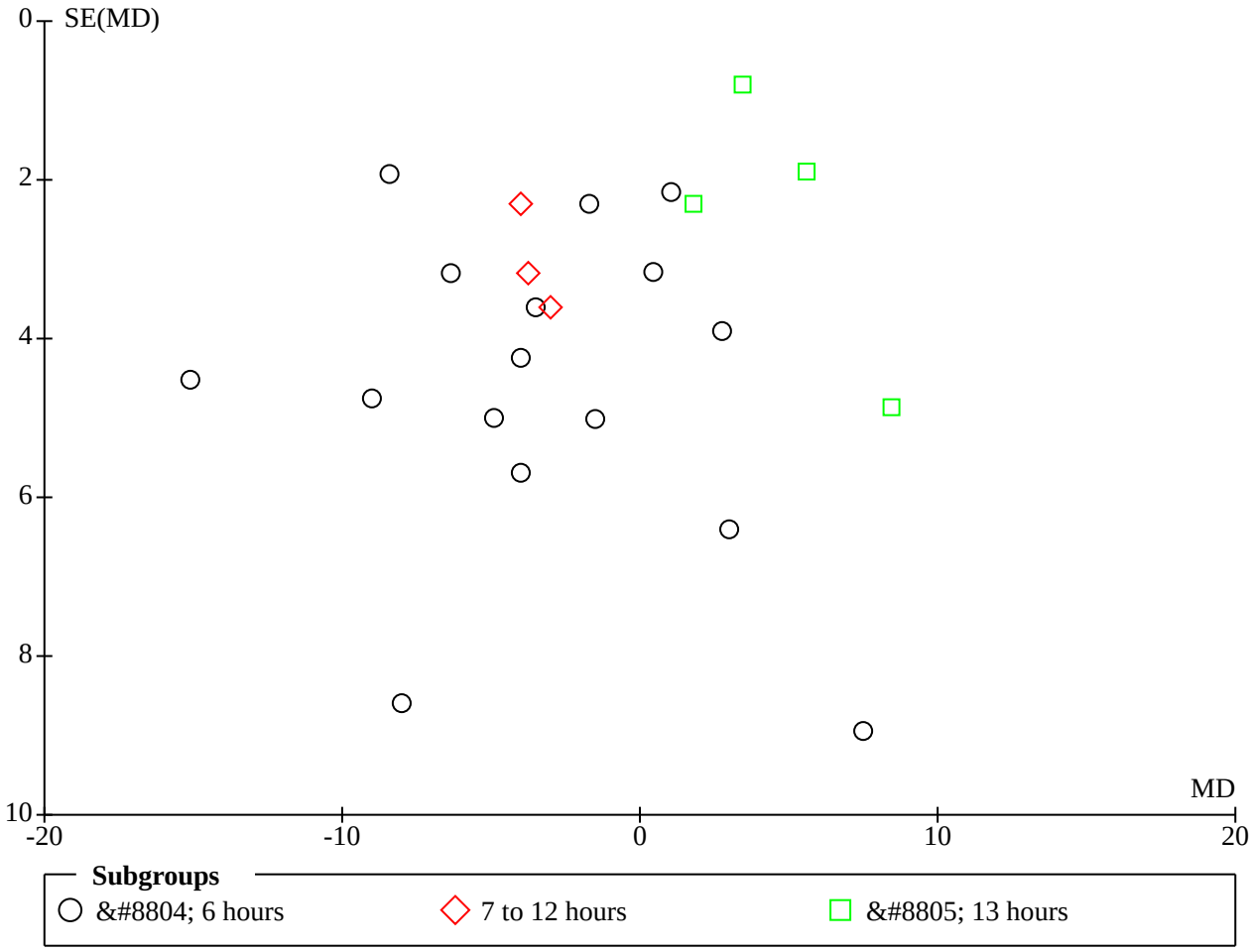


Figure 6. Funnel plot of comparison: 3 High-dose alcohol vs placebo, outcome: 3.2 Diastolic blood pressure.

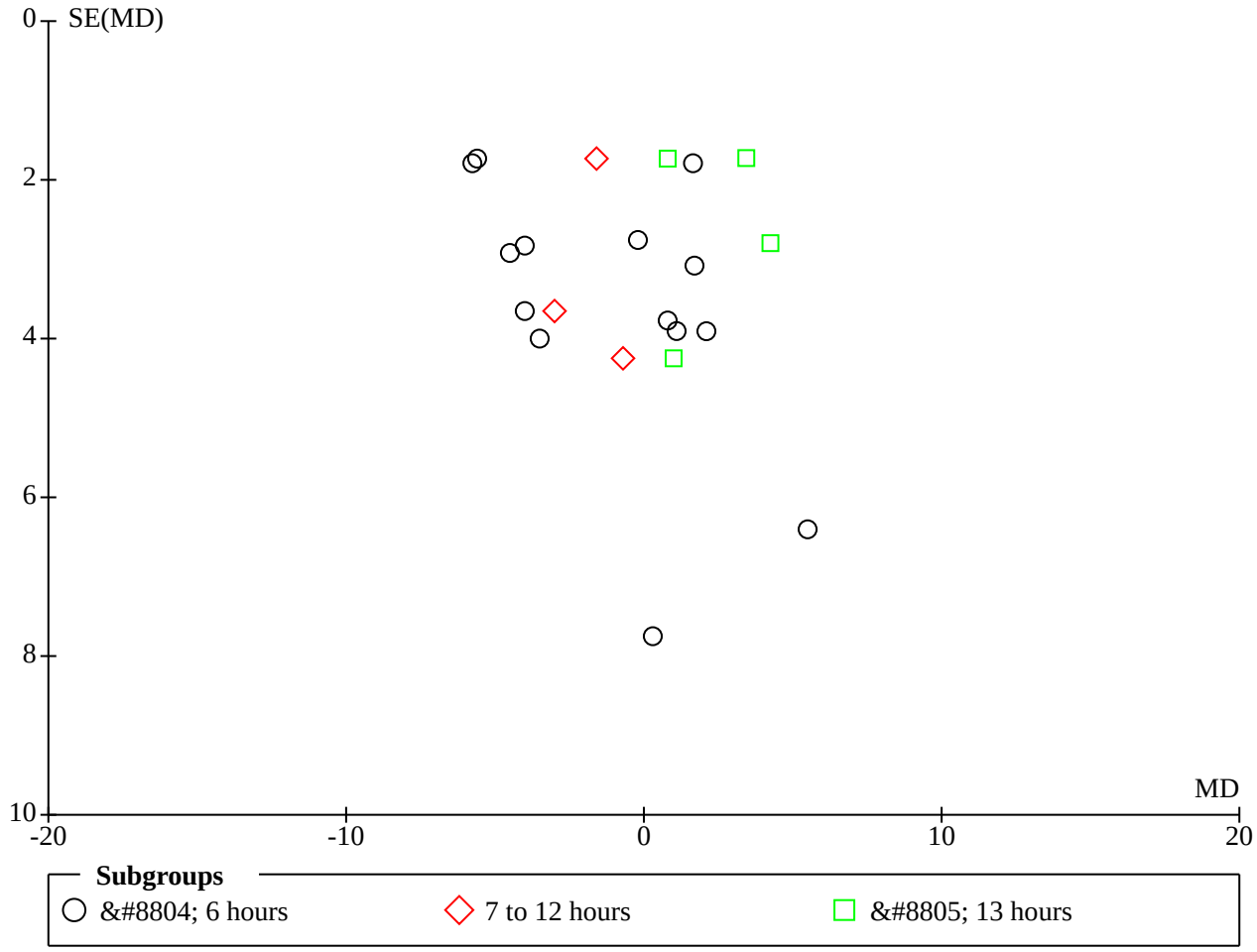


Figure 7. Funnel plot of comparison: 3 High-dose alcohol vs placebo, outcome: 3.3 Mean arterial blood pressure.

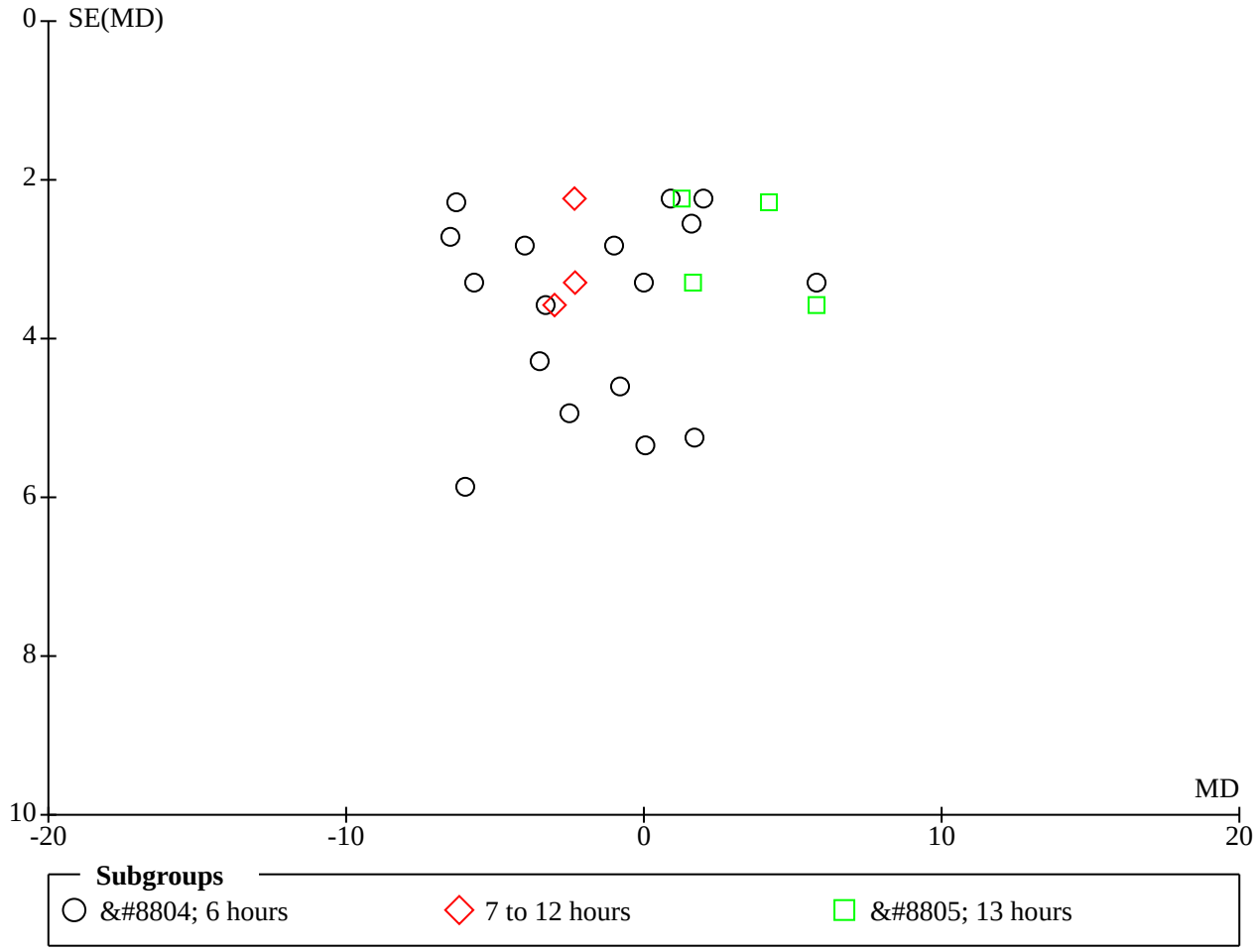


Figure 8. Funnel plot of comparison: 3 High-dose alcohol vs placebo, outcome: 3.4 Heart rate.

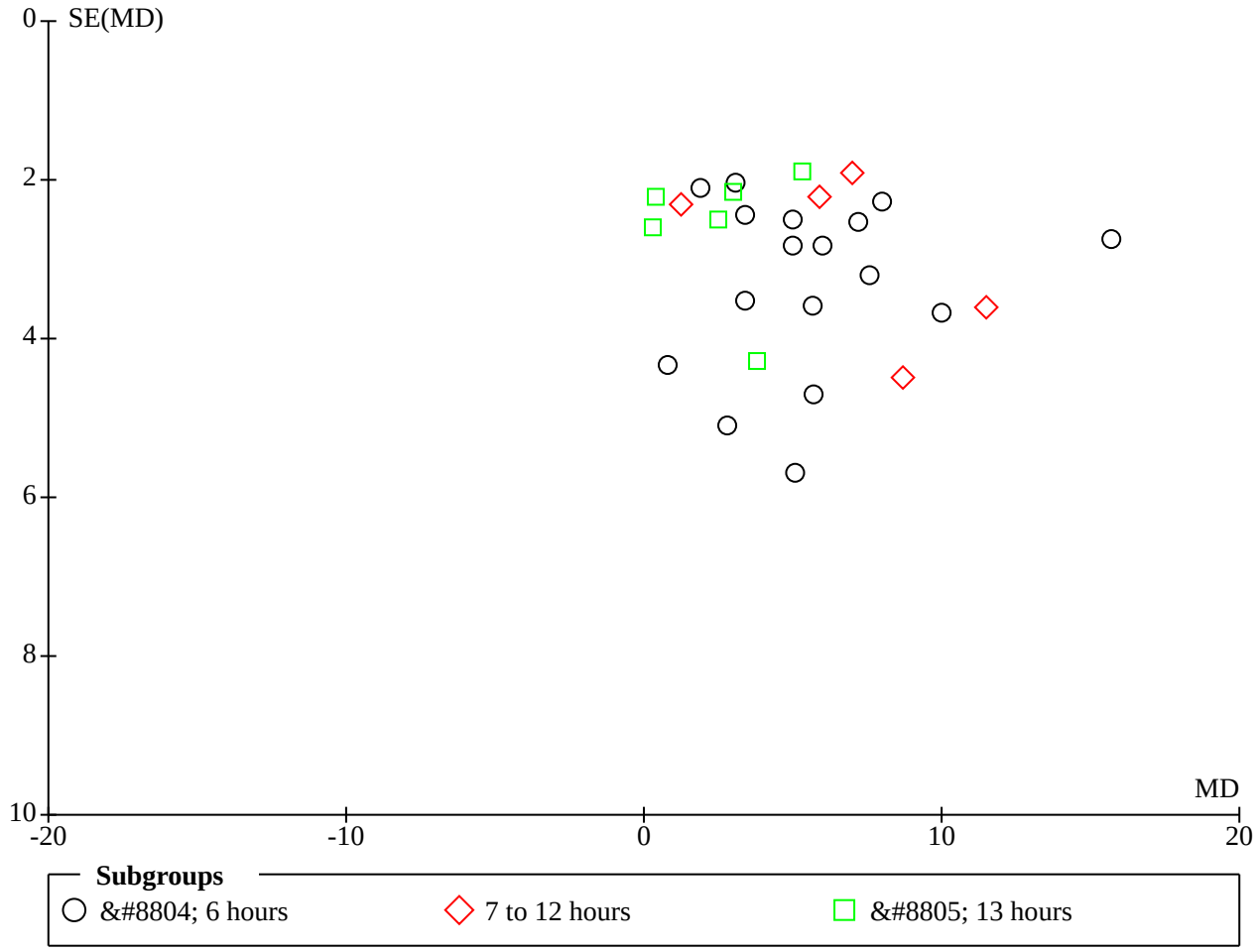


Figure 9. Funnel plot of comparison: 2 Medium-dose alcohol vs placebo, outcome: 2.1 Systolic blood pressure.

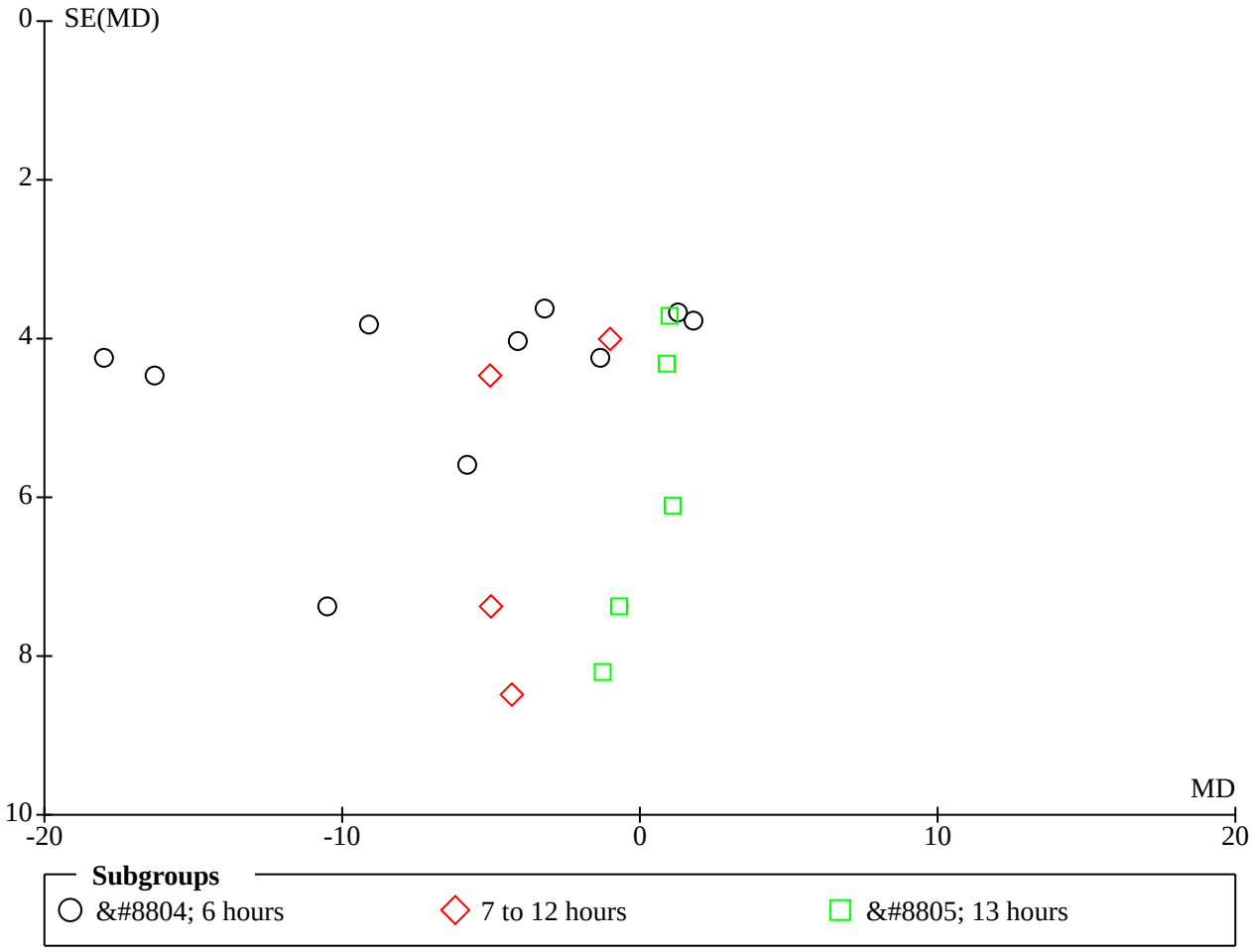


Figure 10. Funnel plot of comparison: 2 Medium-dose alcohol vs placebo, outcome: 2.2 Diastolic blood pressure.

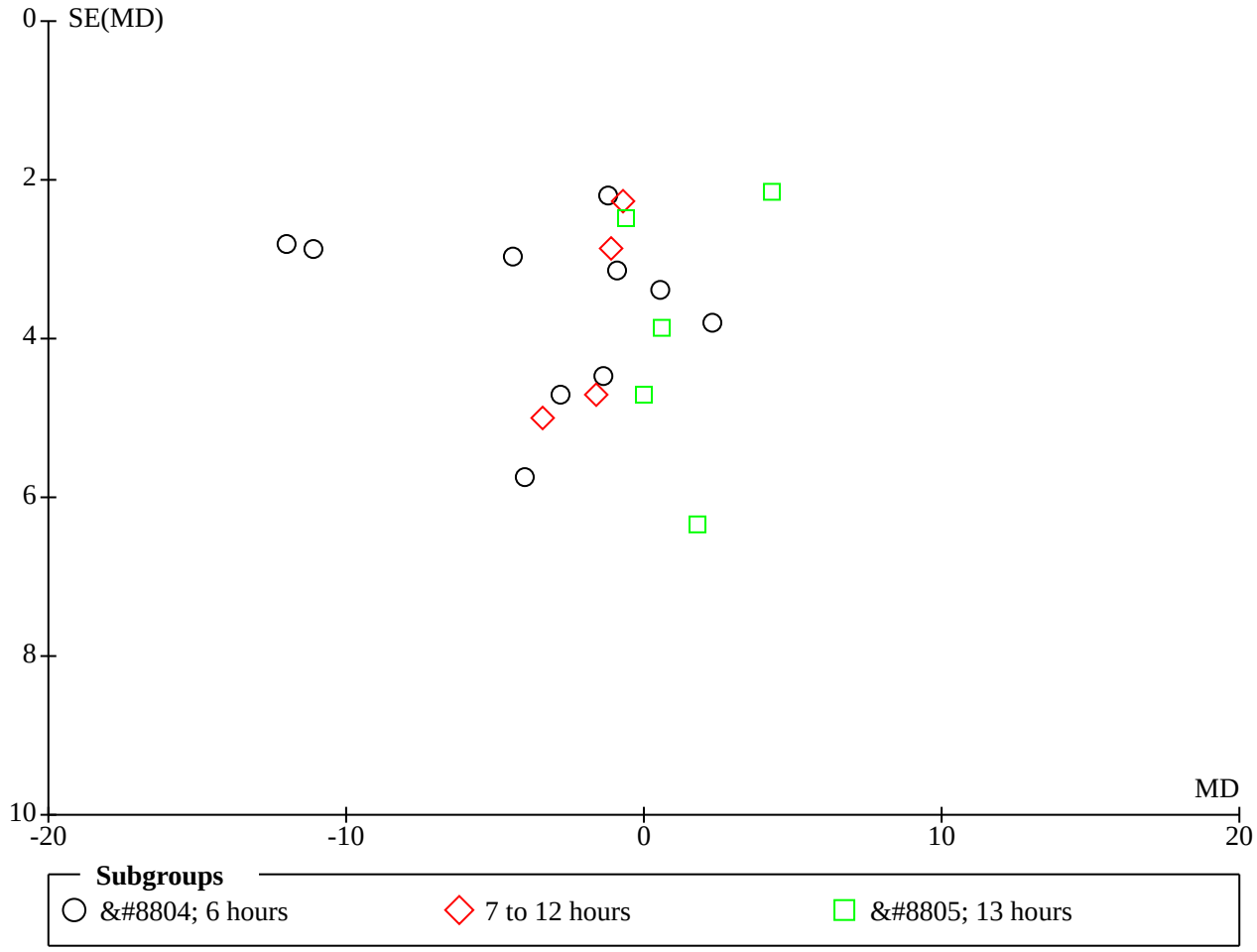
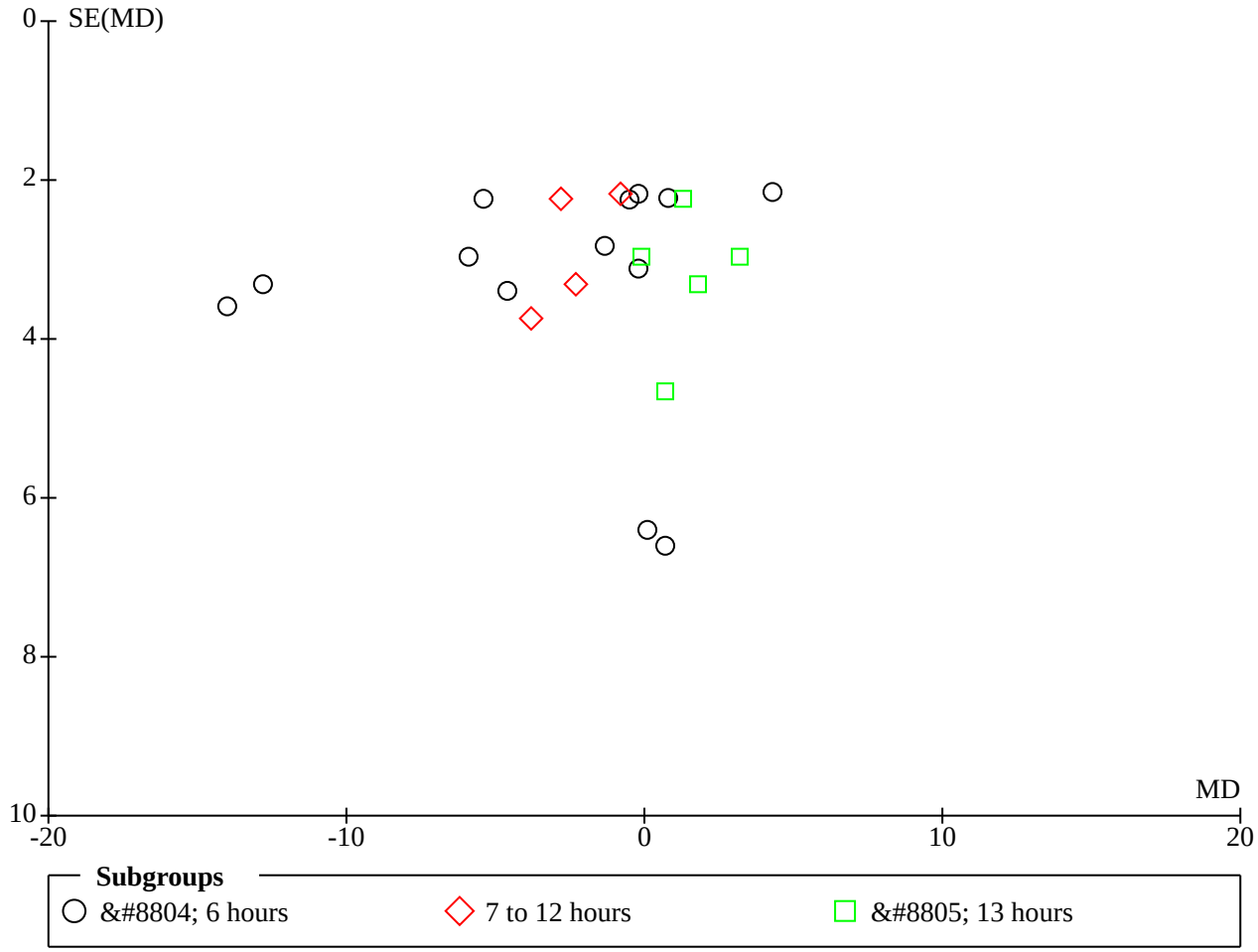


Figure 11. Funnel plot of comparison: 2 Medium-dose alcohol vs placebo, outcome: 2.3 Mean arterial blood pressure.



Effects of interventions

See: **Summary of findings 1** Effect of high-dose alcohol compared to placebo ; **Summary of findings 2** Effect of medium-dose alcohol compared to placebo; **Summary of findings 3** Effect of low-dose alcohol compared to placebo

Low dose

A dose of 14 grams of pure alcohol/ethanol or less was defined as a low dose of alcohol.

Effects of low doses of alcohol on SBP

- ≤ 6 hours after alcohol consumption: based on two studies in 28 participants (Cheyne 2004; Nishiwaki 2017), the mean decrease in SBP with a fixed-effect model was 1.46 mmHg (95% confidence interval (CI) -8.38 to 5.42; P = 0.67). There was no heterogeneity (I^2 = 0%)
- 7 to 12 hours after alcohol consumption: unfortunately, none of the included studies reported results at this time interval
- ≥ 13 hours of alcohol consumption: unfortunately, none of the included studies reported results at this time interval.

Effects of low doses of alcohol on DBP

- ≤ 6 hours after alcohol consumption: two studies reported the early effect of alcohol consumption on DBP; the decrease in DBP was 1.46 mmHg (95% CI -6.91 to 3.99; P = 0.36) (Cheyne 2004; Nishiwaki 2017). There was no heterogeneity (I^2 = 0%)
- 7 to 12 hours after alcohol consumption: unfortunately, none of the included studies reported data at this time interval
- ≥ 13 hours of alcohol consumption: unfortunately, none of the included studies reported data at this time interval

Effects of low doses of alcohol on MAP

- ≤ 6 hours after alcohol consumption: based on MAP data from two studies (Cheyne 2004; Nishiwaki 2017), the mean decrease in DBP for MAP was 1.45 mmHg (95% CI -4.55 to 1.65; P = 0.36). There was no heterogeneity (I^2 = 0%)
- 7 to 12 hours after alcohol consumption: unfortunately, none of the included studies reported data at this time interval
- ≥ 13 hours of alcohol consumption: unfortunately, none of the included studies reported data at this time interval

Effects of low doses of alcohol on HR

- ≤ 6 hours after alcohol consumption: based on the early effect of a low dose of alcohol on HR data from two studies (Cheyne 2004; Nishiwaki 2017), HR was increased significantly by 5.06 bpm (95% CI 1.88 to 8.24; P = 0.002). There was no heterogeneity (I^2 = 0%)
- 7 to 12 hours after alcohol consumption: unfortunately, none of the included studies reported data at this time interval
- ≥ 13 hours after alcohol consumption: unfortunately, none of the included studies reported data at this time interval

Medium dose

Effects of medium doses of alcohol on SBP

- ≤ 6 hours after alcohol consumption: based on data from nine studies in 149 participants (Chen 1986; Fantin 2016; Foppa 2002; Karatzi 2005; Kawano 1992; Kawano 2000; Kojima 1993; Nishiwaki 2017; Rosito 1999), a medium dose of alcohol decreased SBP by 5.63 mmHg (95% CI -8.25 to -3.02; P < 0.001). The I^2 statistic value was 63% and the P value for the Chi^2 test was 0.004, indicating substantial heterogeneity across studies.
  - Due to the presence of substantial heterogeneity across studies, we also conducted this analysis using the random-effects model. A medium dose of alcohol decreased SBP by 6.15 mmHg (95% CI -10.55 to -1.75; P = 0.006)
- 7 to 12 hours after consumption: four studies in 54 participants showed that a medium dose of alcohol decreased SBP by 3.22 mmHg (95% CI -8.37 to 1.93; P = 0.22) 7 to 12 hours after consumption of a medium dose of alcohol (Fantin 2016; Foppa 2002; Kawano 1992; Kawano 2000). There was no heterogeneity (I^2 = 0)
- ≥ 13 hours after consumption: based on data for 66 participants from four studies (Foppa 2002; Kawano 1992; Kawano 2000; Rosito 1999), the mean increase in SBP was 0.64 mmHg (95% CI -3.90 to 5.18; P = 0.78). There was no heterogeneity (I^2 = 0)

Effects of medium doses of alcohol on DBP

- ≤ 6 hours after alcohol consumption: based on data from nine studies in 149 participants (Chen 1986; Fantin 2016; Foppa 2002; Karatzi 2005; Kawano 1992; Kawano 2000; Kojima 1993; Nishiwaki 2017; Rosito 1999), a medium dose of alcohol decreased DBP by 4.01 mmHg (95% CI -6.02 to -2.00; P < 0.001). The I^2 statistic value was 59% and the P value for the Chi^2 test was 0.009, indicating substantial heterogeneity across studies.
  - Due to the presence of substantial heterogeneity across studies, we also conducted this analysis using the random-effects model. A medium dose of alcohol decreased DBP by 3.76 mmHg (95% CI -7.02 to -0.50; P = 0.006)
- 7 to 12 hours after alcohol consumption: four studies in 54 participants reported a mean decrease in DBP of 1.19 mmHg (95% CI -4.29 to 1.90; P = 0.45) after 7 to 12 hours after consumption of a medium dose of alcohol (Fantin 2016; Foppa 2002; Kawano 1992; Kawano 2000). There was no heterogeneity (I^2 = 0)
- ≥ 13 hours after alcohol consumption: Based on data from 66 participants in four studies (Foppa 2002; Kawano 1992; Kawano 2000; Rosito 1999), the mean increase in DBP was 1.78 mmHg (95% CI -0.95 to 4.51; P = 0.64). There was no heterogeneity (I^2 = 0)

Effects of medium doses of alcohol on MAP

- ≤ 6 hours after alcohol consumption: based on data from 17 studies in 428 participants (Barden 2013; Bau 2005; Buckman 2015; Dai 2002; Dumont 2010; Hering 2011; Koenig 1997; Mahmud 2002; Maule 1993; Narkiewicz 2000; Potter 1986; Rosito 1999; Rossinen 1997; Stott 1987; Stott 1991; Williams 2004; Zeichner 1985), we found that a high dose of alcohol decreased MAP by 1.53 mmHg (95% CI -3.34 to 0.28; P = 0.10). There was evidence of low heterogeneity across studies (I^2 = 27%)
  - Due to the presence of substantial heterogeneity across studies, we also conducted this analysis using the random-effects model. A medium dose of alcohol decreased MAP by 2.92 mmHg (95% CI –5.76 to -0.07; P = 0.04)
- 7 to 12 hours after alcohol consumption: based on data from four studies in 54 participants (Fantin 2016; Foppa 2002; Kawano 1992; Kawano 2000), the mean decrease in MAP was 2.11 mmHg (95% CI -4.69 to 0.48; P = 0.11) after 7 to 12 hours after consumption of a medium dose of alcohol. There was no heterogeneity (I^2 = 0)
- ≥ 13 hours after alcohol consumption: based on data from 66 participants from four studies (Foppa 2002; Kawano 1992; Kawano 2000; Rosito 1999), the mean increase in MAP was 1.43 mmHg (95% CI -1.18 to 4.04; P = 0.28). There was no heterogeneity (I^2 = 0)

Effects of medium doses of alcohol on HR

- ≤ 6 hours after alcohol consumption: 12 studies reported the effects of alcohol consumption in 181 participants (Agewall 2000; Chen 1986; Fantin 2016; Fazio 2004; Foppa 2002; Karatzi 2005; Karatzi 2013; Kawano 1992; Kawano 2000; Kojima 1993; Maufrais 2017; Nishiwaki 2017); the mean increase in HR was 4.62 bpm (95% CI 3.14 to 6.11; P < 0.01). There was no heterogeneity (I^2 = 0)
- 7 to 12 hours after alcohol consumption: based on data from four studies in 54 participants (Fantin 2016; Foppa 2002; Kawano 1992; Kawano 2000), the mean increase in HR was 1.22 bpm (95% CI –1.88 to 4.32; P = 0.44) after 7 to 12 hours after consumption of a medium dose of alcohol. There was no heterogeneity (I^2 = 0)
- ≥ 13 hours after alcohol consumption: based on three studies in 36 participants (Foppa 2002; Kawano 1992; Kawano 2000), the mean increase in HR was 1.37 bpm (95% CI -2.12 to 4.86; P = 0.44)

High dose

Effects of high doses of alcohol on SBP

- ≤ 6 hours after alcohol consumption: based on data from 418 participants in 16 studies (Barden 2013; Bau 2005; Buckman 2015; Dai 2002; Hering 2011; Koenig 1997; Mahmud 2002; Maule 1993; Narkiewicz 2000; Potter 1986; Rosito 1999; Rossinen 1997; Stott 1987; Stott 1991; Williams 2004; Zeichner 1985), high doses of alcohol decreased SBP by 3.49 mmHg (95% CI -6.03 to -0.95; P = 0.007). The I^2 statistic value was 45% and the P-value for the Chi^2 test was 0.02, indicating moderate heterogeneity across studies
- 7 to 12 hours after alcohol consumption: based on data from 54 participants in three studies (Barden 2013; Rosito 1999; Stott 1987), high doses of alcohol decreased SBP by 3.72 mmHg (95% CI -6.97 to -0.48; P = 0.02). There was no heterogeneity (I^2 = 0)

- ≥ 13 hours after alcohol consumption: based on data from 154 participants in four studies (Barden 2013; Bau 2005; Rosito 1999; Stott 1987), high doses of alcohol increased SBP by 3.69 mmHg (95% CI 2.33 to 5.05; P < 0.001]. There was no heterogeneity (I^2 = 0)

Effects of high doses of alcohol on DBP

- ≤ 6 hours after alcohol consumption: based on data from 350 participants in 14 studies (Barden 2013; Bau 2005; Dai 2002; Hering 2011; Koenig 1997; Mahmud 2002; Maule 1993; Narkiewicz 2000; Potter 1986; Rosito 1999 ; Stott 1987; Stott 1991; Williams 2004; Zeichner 1985), high doses of alcohol decreased DBP by 1.91 mmHg (95% CI -3.86 to 0.04; P = 0.05). The I^2 statistic value was 35% and the P-value for the Chi^2 test was < 0.1, indicating low heterogeneity across studies
- 7 to 12 hours after alcohol consumption: based on data from 54 participants in three studies (Barden 2013; Rosito 1999; Stott 1987), high doses of alcohol decreased DBP by 1.71 mmHg (95% CI –4.59 to 1.77; P = 0.24). There was no heterogeneity (I^2 = 0)
- ≥ 13 hours after alcohol consumption: based on data from 154 participants in four studies (Barden 2013; Bau 2005; Rosito 1999; Stott 1987), high doses of alcohol increased DBP by 2.37 mmHg (95% CI 0.24 to 4.49; P = 0.03) after 13 hours of consumption. There was no heterogeneity (I^2 = 0)

Effects of high doses of alcohol on MAP

- ≤ 6 hours after alcohol consumption: based on data from 16 studies in 418 participants (Barden 2013; Bau 2005; Buckman 2015; Dai 2002; Dumont 2010; Hering 2011; Koenig 1997; Mahmud 2002; Maule 1993; Narkiewicz 2000; Potter 1986; Rosito 1999; Stott 1987; Stott 1991; Williams 2004; Zeichner 1985), high doses of alcohol decreased MAP by 1.79 mmHg (95% CI -3.72 to 0.13; P = 0.07). There was evidence of low heterogeneity across studies (I^2 = 30%)
- 7 to 12 hours after alcohol consumption: three studies reported the effects of high doses of alcohol consumption in 54 participants (Barden 2013; Rosito 1999; Stott 1987); the mean decrease in MAP was 2.47 mmHg (95% CI -5.69 to 0.75; P = 0.13). There was no heterogeneity (I^2 = 0)
- ≥ 13 hours after alcohol consumption: four studies reported the effects of high doses of alcohol in 154 participants (Barden 2013; Bau 2005; Rosito 1999; Stott 1987); the mean increase in MAP was 2.96 mmHg (95% CI 0.35 to 5.58, P = 0.02) ≥ 13 hours after consumption. There was no heterogeneity (I^2 = 0)

Effects of high doses of alcohol on HR

- ≤ 6 hours after alcohol consumption: 17 studies reported the effects of high doses of alcohol in 495 participants (Barden 2013; Bau 2005; Bau 2011; Buckman 2015; Dai 2002; Dumont 2010; Hering 2011; Maule 1993; Narkiewicz 2000; Potter 1986; Rosito 1999; Rossinen 1997; Stott 1987; Stott 1991; Van De Borne 1997; Williams 2004; Zeichner 1985); the mean increase in HR was 5.75 bpm (95% CI 3.99 to 7.51; P < 0.001). There was evidence of low heterogeneity across studies (I^2 = 34%)
- 7 to 12 hours after alcohol consumption: five studies reported the effects of high doses of alcohol in 144 participants (Barden 2013; Bau 2011; Rosito 1999; Rossinen 1997; Stott 1987); the mean increase in HR was 6.16 bpm (95% CI 3.04 to 9.28; P < 0.001). There was moderate heterogeneity across studies (I^2 = 44%)
- ≥ 13 hours after alcohol consumption: six studies reported the effects of high doses of alcohol in 244 participants (Barden 2013; Bau 2005; Bau 2011; Rosito 1999; Rossinen 1997; Stott 1987); the mean increase in HR was 2.70 bpm (95% CI 0.80 to 4.60; P = 0.005) ≥ 13 hours after consumption. There was no heterogeneity (I^2 = 0)

The above-mentioned results are summarised in Summary of findings 1, Summary of findings 2, and Summary of findings 3.

Subgroup analysis

It is recommended that there should be at least 10 studies reporting each of the subgroups in question. Among the 32 included studies, only four studies included hypertensive participants (Kawano 1992; Kawano 2000; Kojima 1993; Foppa 2002). So, it was not appropriate to conduct a separate meta-analysis based on that population.

For the planned subgroup analysis based on sex, no studies reported male and female participant data separately. Therefore, we were unable to perform a subgroup analysis based on the sex of participants.

Sensitivity analysis

As planned, we conducted sensitivity analyses to see if there was any significant difference between effect estimates of outcomes given by the fixed-effect model and the random-effects model, when substantial heterogeneity was present. The result is presented in Table 3; there was no significant difference between results given by the two models.

We planned on conducting sensitivity analyses on studies based on their level of risk of bias (high-risk studies versus low-risk studies). Most of the included studies had similar risk of bias across all domains except for performance bias and detection bias, for which risk arises from blinding of participants, personnel, and outcome assessors. So, we decided to conduct a sensitivity analysis of the included studies based on the blinding condition (Table 4). We observed a greater reduction in blood pressure after a moderate dose of alcohol consumption for the unblinded studies, which was probably due to the presence of a heterogeneous population. For high-dose alcohol studies, we did not find any significant difference between blinded and unblinded studies. Overall, the of studies did not influence outcomes.

DISCUSSION

This review summarises the acute effects of different doses of alcohol on blood pressure and heart rate in adults (≥ 18 years of age) during three different time intervals after ingestion of alcohol.

Summary of main results

Effects of low-dose alcohol consumption

Low-dose alcohol consumption had no effect on blood pressure (BP) within six hours, but we found only two trials that studied this dose and no trials that assessed BP after six hours. Low-dose alcohol increased heart rate (HR) within six hours, suggesting that even one glass of wine increases HR. Unfortunately, we found no studies measuring HR more than six hours after the dose.

Effects of medium-dose alcohol consumption

Medium-dose alcohol decreased systolic blood pressure (SBP) by 5.6 mmHg and diastolic blood pressure (DBP) by 4 mmHg within the

first six hours of consumption. Although the hypotensive effect of alcohol seemed to last up to 12 hours after drinking alcohol, and the effect was lost after 13 hours, the result was based on only four trials reporting intermediate (7 to 12 hours) and late (after 13 hours) effects of alcohol on BP.

Heart rate was increased by 4.6 bpm six hours after drinking alcohol compared to placebo. Intermediate (7 to 12 hours) and late (after 13 hours) effects of the medium dose of alcohol on HR were based on only four trials and were not statistically different compared to placebo.

Effects of high-dose alcohol consumption

High-dose alcohol decreased SBP by 3.49 mmHg within the first six hours, and by 3.77 mmHg between 7 and 12 hours after consumption. After 13 hours, high doses of alcohol increased SBP by 3.7 mmHg compared to placebo. DBP was not significantly affected up to 12 hours after drinking a high dose of alcohol, but there was a statistically significant increase in DBP during the ≥ 13 hour time interval after alcohol consumption.

High-dose alcohol consumption increased HR by approximately 6 bpm in participants, and the effect lasted up to 12 hours. After that, HR was still raised in participants, but it averaged 2.7 bpm.

Dose-dependent response

There is likely a dose-response effect of alcohol on BP, as the effects of alcohol appeared to last longer with higher doses. However, we lacked data on the effects of low doses. We intended to find out the dose-dependent changes in SBP, DBP, mean arterial pressure (MAP), and HR after consumption of a single dose of alcohol. Because the numbers of included studies that fell into our pre-specified dose categories were not comparable, we were unable to conduct a comprehensive dose-dependent analysis. Rosito 1999 tested the effects of 15 g, 30 g, and 60 g of alcohol on 40 young medical students. The decrease in SBP was greater with 30 g of alcohol seven hours after consumption compared to placebo and 15 g and 60 g alcohol-consuming groups. In this study, alcohol had no significant effect on DBP in the four groups.

Possible mechanisms to explain the results

Many interrelated changes are possibly responsible for the biphasic effect of alcohol on blood pressure.

Acute alcohol consumption was found to reduce 20-hydroxyeicosatetraenoic acid (20-HETE) in Barden 2013. 20-HETE is a signalling molecule with a wide range of effects on the cardiovascular system. It is a vasoconstrictor that inhibits sodium reabsorption in the proximal and distal tubules of the kidney. The reduction in 20-HETE was greatest when the blood alcohol level was highest (Barden 2013; Collins 2005). Increased production of nitric oxide (NO) was also associated with acute alcohol consumption (Deng 2007; Rocha 2012). NO is released from the endothelium and is a potent vasodilator. Also, there is an inverse relationship between NO and 20-HETE. Alcohol is often consumed mixed together with fruit juices, and the combination was found to promote insulin secretion (Steiner 2015). Insulin is known to signal a phosphorylation-dependent mechanism resulting in the production of NO (Muniyappa 2007). Moreover, alcohol's metabolic byproduct acetaldehyde is another known vasodilator (Altura 1978; Gillespie 1967). Together, the reduction in vasoconstrictors and the increase in vasodilators could be the explanation for the drop in blood pressure, which lasted approximately 12 hours.

The blood alcohol level decreased over time, and 20-HETE started to rise (Barden 2013). The hypertensive effect of alcohol after 13 hours of consumption could be the result of the rise in vasoconstrictors and the homeostatic response to restore blood pressure. Plasma renin activity was reported to be increased in Kawano 2000 as a late effect of alcohol consumption.

Heart rate was increased following alcohol consumption regardless of the dose of alcohol. Alcohol has been shown to slow down parasympathetic nervous activity and to stimulate sympathetic nervous activity. Hering 2011, Carter 2011, and Spaak 2008 reported an increase in muscle sympathetic nervous activity (MSNA), which persists for at least 10 hours after consumption. The vagus nerve is a component of the parasympathetic nervous system and is largely responsible for regulation of the heart rate at rest. Rossinen 1997 and Van De Borne 1997 reported withdrawal of vagal tone and reduced heart rate variability within an hour after alcohol consumption; this explains the increased heart rate. Buckman 2015, Van De Borne 1997, and Fazio 2001 also reported reduced baroreflex sensitivity following alcohol consumption. Impairment of baroreflex sensitivity results in failure to sense the increase in heart rate and maintenance of cardiovascular homeostasis. Kawano 2000 reported a reduction in plasma potassium levels after alcohol consumption, which might provide another reason for the increase in heart rate.

Clinical implications of the findings

This systematic review provides us with a better understanding of the time-course of alcohol's acute effects on blood pressure and heart rate. This review included only short-term randomised controlled trials (RCTs) investigating the effects of alcohol on blood pressure and heart rate. Acute alcohol consumption mimics the pattern of social drinking, and evidence indicates that even one glass of an alcoholic drink can increase heart rate. The magnitude of the effects of alcohol on blood pressure and heart rate varies, based possibly on genetic factors and on the amount of alcohol consumed.

Several long-term observational studies have reported that light to moderate alcohol consumption is associated with a reduction in adverse cardiovascular events (Briasoulis 2012; Di Castelnuovo 2006; Plunk 2014; Taylor 2009). At the present time, the explanation for these possible beneficial effects of regular light to moderate alcohol consumption is unknown. In this review, consuming medium (moderate) doses of alcohol lowered blood pressure for possibly up to 12 hours after consumption. Perhaps regular light to moderate consumption of alcohol lowers blood pressure, and this is the explanation for the reduction in cardiovascular events seen in the observational studies.

On the other hand, this review shows that high doses of alcohol increased blood pressure after 13 hours and could lead to increased blood pressure the day after consumption. Thus regular consumption of high doses of alcohol could lead to a sustained increase in blood pressure and the adverse consequences associated with hypertension.

Hypertensive individuals who take antihypertensive drugs should be cautious about the timing of drinking alcohol because the

combination of some antihypertensive drugs and alcohol was found to synergistically reduce blood pressure (Bailey 1989; Kawano 1999; Kawano 2000).

Overall completeness and applicability of evidence

The evidence synthesised in this review was collected from 32 RCTs in 767 participants. Of the 32 studies, two studied low-dose alcohol, 12 studied medium-dose alcohol, and 19 studied high-dose alcohol. Rosito 1999 studied both medium and high doses of alcohol. The sample size in the meta-analysis for low-dose comparison was not adequate to assess the effects of low doses of alcohol on BP and HR; however, we believe that the direction of the change in BP and HR was correct. For medium doses and high doses of alcohol, participants represented a range in terms of age, sex, and health condition. Because the participant population comprised predominantly young and healthy normotensive men, the overall evidence generated in this review cannot be extrapolated to women and older populations with other comorbidities.

There was substantial heterogeneity in the meta-analysis for effects of medium doses on SBP and DBP six hours after alcohol consumption (Analysis 2.1 and Analysis 2.2) due to the inclusion of Kawano 1992, Kawano 2000, and Kojima 1993. Participants in these studies were Japanese with mean age > 50 years and essential hypertension. The mean reduction in SBP and DBP was greater in these participants compared to participants from other studies ingesting medium doses of alcohol. The reason behind the greater reduction in blood pressure after consuming alcohol is probably the presence of genetic variants of the hormones alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) among Japanese participants. The presence of these gene variants can cause an increase in the blood acetaldehyde level to more than 10 times the normal level (Enomoto 1991; Peng 2014; Thomasson 1995). The ALDH2*2 allele is a gene variant of the enzyme ALDH and is almost exclusively present in the northeast Asian population (Wall 2016). Studies on liver extracts have reported that this particular allele of ALDH is dominant. The presence of this allele leads to reduced acetaldehyde metabolising activity in heterozygotes and no metabolising activity in homozygotes (Li 2009; Li 2012). In both cases, the blood acetaldehyde level after alcohol consumption was found to be greater than the normal range. An excessive amount of acetaldehyde in blood is responsible for facial flushing, which is a common adverse effect of alcohol consumption among east Asians. Acetaldehyde could be responsible for the hypotensive effects of alcohol (Altura 1978; Gillespie 1967), and excessive acetaldehyde could be the reason for the greater reduction in blood pressure reported in the aforementioned studies including Japanese populations.

To check whether the age of participants had any role in the effects of alcohol on blood pressure, we selected studies with older participants (> 50 years) from the analysis (Analysis 2.1; Analysis 2.2; Analysis 3.1; Analysis 3.2). Studies with older participants showed a greater decrease in SBP and DBP compared to studies with younger participants (< 50 years) (results presented in Table 5). Although we do not have much confidence in the mean change in blood pressure in the older population due to fewer studies compared to studies with younger participants and the presence of heterogeneity, previous research suggests that age can affect the rate of elimination of alcohol from the body (Cederbaum 2012; Hahn 1983). With increasing age, the amount of body water and liver mass are decreased, leading to higher blood alcohol levels. Also, the metabolising enzymes such as cytochrome P-4502E1 and ALDH diminish with age. Older populations are more likely to take more drugs to treat existing comorbidities, and the drug-alcohol interaction can modify alcohol metabolism (Meier 2008). All these factors can lead to increased acetaldehyde in the body and greater reduction in blood pressure.

Rosito 1999 reported the effects of 15, 30, and 60 g of alcohol compared to placebo on healthy male volunteers. According to our pre-specified dose categories, both 15 g and 30 g of alcohol fell under the medium dose category. Including both of these doses or de-selecting either one of these doses from Rosito 1999 from Analysis 2.1 and Analysis 2.2 (medium doses of alcohol) resulted in the same statistically significant conclusion.

We identified Stott 1987 and Barden 2013 from Analysis 3.1 and Analysis 3.2 as having a considerably lower standard error (SE) of the mean difference (MD) compared to the other included studies. Assuming that the low SEs of MDs reported in Stott 1987 and Barden 2013 are errors and are not reliable, we replaced these measures with the average SE of MD from the rest of the included studies. The statistically significant conclusions remained the same.

Nine out of the 19 studies used comparatively high (≥ 60 g or ≥ 1 g/kg) doses of alcohol compared to the 10 other studies under the high dose of alcohol category, and consumption of very high doses of alcohol in these nine trials over the reported short duration mimics the pattern of binge drinking. Hence, we conducted additional analyses to see if the very high dose of alcohol (≥ 60 g or ≥ 1 g/kg) had any dose-related effects compared to lower high doses of alcohol (31 to 59 g of alcohol) (see Table 6). Results suggest that the decrease in BP with very high doses of alcohol is greater compared to lower high doses of alcohol. The change in heart rate was similar in both comparisons. However, the result was heterogeneous; therefore, we are unable to make any implications from this.

This is the first systematic review on this topic based on RCTs. Much of the current literature on alcohol does not mention the hypotensive effect of alcohol or the magnitude of change in BP or HR after alcohol consumption. This review will be useful for social and regular drinkers to appreciate the risks of low blood pressure within the first 12 hours after drinking.

Quality of the evidence

We graded the overall certainty of evidence using the GRADE approach via GRADEpro GDT software (GRADEpro 2014); we formulated summary of findings (SoF) tables.

We created three SoF tables to show the certainty of evidence and the summary of effects on outcomes of interest (SBP, DBP, and HR) for high (Summary of findings 1), medium (Summary of findings 2), and low doses (Summary of findings 3) of alcohol.

Ratings of the certainty of evidence ranged from moderate to low in this review, which suggests that the effect estimates of alcohol might be slightly different than the true effects. For high doses of alcohol, we found moderate-certainty evidence showing a decrease in SBP and low-certainty evidence suggesting a decrease in DBP within the first six hours and 7 to 12 hours after consumption.

Moderate-certainty evidence shows that SBP and DBP rise between 13 and 24 hours after alcohol ingestion.

For medium doses of alcohol, moderate-certainty evidence shows a decrease in SBP and DBP six hours after alcohol consumption, and low-certainty evidence suggests a decrease in SBP and DBP for 7 to 12 hours after alcohol consumption. After ≥ 13 hours of consumption, SBP and DBP were raised; the certainty of evidence was low and medium, respectively.

For low doses of alcohol, we found low-certainty evidence suggesting that SBP, DBP, and MAP fall within the first six hours after alcohol consumption.

We also found moderate-certainty evidence showing that alcohol raises HR within the first six hours of consumption, regardless of the dose of alcohol. Moderate-certainty evidence indicates an increase in heart rate after 7 to 12 hours and ≥ 13 hours after high-dose alcohol consumption, low certainty of evidence was found for moderate dose of alcohol consumption.

We did not consider the lack of blinding of participants as a downgrading factor for certainty of evidence because we do not think that it affected the outcomes of this systematic review. Changes in blood pressure and heart rate after alcohol consumption were not the primary outcomes of interest in most of the included studies. We do not think participants were anticipating any significant influence on blood pressure or heart rate after drinking.

We also did not rate the certainty of evidence based on the funding sources of studies or on lack of a registered protocol because we did not think this would affect the effect estimates for these outcomes. However, we noted the lack of description of randomisation and allocation concealment methods in most of the included studies as a reason for downgrading because of the possibility of selection bias.

Potential biases in the review process

We faced several limitations during the review process. First, there was the possibility of undesired bias and imprecision due to imputations of missing statistics. Most of the included studies did not report the standard error (SE)/standard deviation (SD) of the mean difference (MD) for the outcomes of interest. As described in our protocol, when we were unable to obtain the required SE/SD from study authors or by calculation from the reported P value or 95% CI, we imputed data according to the pre-specified imputation hierarchy. We most often used the reported endpoint SE/SD value to impute the SE/SD of MD. This is known to provide a good approximation of the SD of change in BP so is unlikely to lead to bias. Also, only 10 out of 32 studies reported changes in MAP after alcohol consumption along with SE/SD (Buckman 2015; Dumont 2010; Foppa 2002; Karatzi 2005; Karatzi 2013; Kojima 1993; Maufrais 2017; Maule 1993; Narkiewicz 2000; Van De Borne 1997). So, we had to calculate missing MAP values from reported SBP and DBP values using the formula mentioned in the protocol and we imputed the SE/SD for those.

Second, lack of representation of the female population was notable in the included studies. Only 16 out of 32 studies included a total of 129 (16% of total participants) female participants (Agewall 2000; Buckman 2015; Chen 1986; Cheyne 2004; Dumont 2010; Fantin 2016; Foppa 2002; Hering 2011; Mahmud 2002; Maufrais 2017; Maule 1993; Narkiewicz 2000; Rossinen 1997; Stott 1987; Stott 1991; Zeichner 1985), and this number was very low compared to 638 male participants. Only four studies included almost equal numbers of male and female participants (Buckman 2015; Foppa 2002; Maufrais 2017; Zeichner 1985). Moreover, none of the studies reported male and female data separately. As a result, we were not able to quantify the magnitude of the effects of alcohol on men and women separately. This is unfortunate, as we have reason to believe that the effects of alcohol on BP might be greater in women.

Methodological differences between studies might have affected measurement of the reported outcomes. Recent research suggests that automated ambulatory blood pressure monitors are more reliable than manual sphygmomanometers, particularly because automated monitors reduce white coat anxiety (Mirdamadi 2017). Of the 32 included studies, seven studies used a manual mercury sphygmomanometer or a semi-automated sphygmomanometer for BP measurement (Bau 2005; Dai 2002; Karatzi 2005; Kojima 1993; Potter 1986; Rossinen 1997; Van De Borne 1997). Mixing of various measurement techniques (manual, semi-automated, and fully automated) in the meta-analysis might have led to some of the heterogeneity.

Another reason behind the heterogeneity was probably the variation in alcohol intake duration and in the timing of measurement of outcomes across the included studies. Most studies gave participants 15 to 30 minutes to finish their drinks, started measuring outcomes sometime after that, and continued taking measurements for a certain period, but there were some exceptions. Chen 1986 did not report consumption duration nor timing of measurement of BP and HR. Dai 2002 gave participants five minutes to consume high doses of alcohol and measured outcomes immediately. On the other hand, Fantin 2016 allowed participants to continue drinking during the period of outcome measurement. These differences in alcohol consumption duration and in outcome measurement times probably contributed to the wide variation in blood pressure in these studies and affected overall results of the meta-analysis.

We took several steps to minimise the risk of selection bias to identify eligible studies for inclusion in the review. We used highly sensitive search strategies. We also checked the lists of references in the included studies and articles that cited the included studies in Google Scholar to identify relevant articles. Furthermore, we contacted authors of included studies to obtain all relevant data when information was insufficient or missing.

Agreements and disagreements with other studies or reviews

We are aware of one systematic review on effects of alcohol on blood pressure that was published in 2005 (McFadden 2005). McFadden 2005 included both randomised and non-randomised studies with a minimum of 24 hours of blood pressure observation after alcohol consumption. This systematic review searched only the MEDLINE database for relevant studies, hence it was not exhaustive. Review authors included nine studies involving a total of 119 participants, and the duration of these studies was between four and seven days. Participants in those studies consumed alcohol regularly during the study period, whereas in our systematic review, we included only studies in which participants consumed alcohol for a short period. Based on nine studies, McFadden 2005 reported that the mean increase in SBP

was 2.7 mmHg and in DBP was 1.4 mmHg. Only three of these studies measured BP at various time points and found that alcohol has a hypotensive effect lasting up to five hours after alcohol consumption and a hypertensive effect 20 hours after alcohol consumption that lasts until the next day. These findings are consistent with our results. However, the reported early reduction in BP was 11. 6 mmHg for SBP and 7.9 mmHg for DBP in McFadden 2005. These estimates are almost twice as large as our results. The inclusion of non-randomised studies in McFadden 2005, which are known to be at higher risk of bias, is likely the reason for the discrepancy in the magnitude of BP effects.

AUTHORS' CONCLUSIONS

Implications for practice

The magnitude and direction of the effects of alcohol on blood pressure depend on the time after alcohol consumption. Moderate-certainty evidence shows that acute consumption of medium to high doses of alcohol decreases blood pressure within the first six hours and for up to 12 hours after alcohol consumption. For times greater than 13 hours, high doses of alcohol consumption increased blood pressure. Low, moderate, and high alcohol consumption increased heart rate within the first six hours. High alcohol consumption also increased heart rate from 7 to 12 hours and after 13 hours. Most of the evidence from this review is relevant to healthy males, as these trials included small numbers of women (126 females compared to 638 males).

Implications for research

This review did not find any eligible RCTs that reported the effects of alcohol on women separately. Because women could be affected differently by alcohol than men, future RCTs in women are needed. If future RCTs include both men and women, it is important that their blood pressure and heart rate readings are reported separately. Although eligible studies included East Asian, Latino, and Caucasian populations, they lacked African, South Asian, and Native Hawaiian/other Pacific Islander representation. Most of the hypertensive participants in the included studies were Japanese, so it is unclear if the difference in blood pressure between alcohol and placebo groups was due to the presence of genetic variants or the presence of hypertension. Large RCTs including both hypertensive and normotensive participants with various ethnic backgrounds are required to understand the effects of alcohol on blood pressure and heart rate based on ethnicity and the presence of hypertension. More RCTs are needed to study the effects of low-dose alcohol to better delineate the dose-response effects of alcohol on BP and heart rate. RCTs with measurements more than 24 hours after alcohol consumption are needed to see how long the effect of high-dose acute alcohol consumption lasts.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agewall 2000

Study characteristics	
Methods	Randomised controlled trial, single blinded, cross-over design
Participants	12 adult volunteers (8 male and 4 female) with mean age of 31 years were included in the study Inclusion criteria: • Normotensive • Younger than 40 years of age • Non-smoker • Non-diabetic • Normal serum cholesterol • No medications
Interventions	• 250 mL of a Cabernet Sauvignon/Merlot red wine containing 12.5% alcohol by volume (calculated dose: 31.25 g) • De-alcoholised red wine containing < 0.5% alcohol by volume Both were consumed over 10 minutes
Outcomes	• Brachial artery diameter • Arterial flow velocity measurements • Heart rate • Plasma–ethanol Measured at baseline and 60 minutes after consumption of the drink
Notes	• Participants were served a standardised light lunch at noon. Lunch consisted of a baguette filled with 5 g of margarine, 2 leaves of lettuce, half of a sliced tomato, a slice of lean cheese and a little pepper, low-fat yogurt (150 g), and a banana • Washout period was 1 week between interventions

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The subjects drank 250 ml of red wine with or without alcohol over 10 min according to a randomized procedure" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	"Subsequently the subjects were randomly allocated to drink over 10 min either 250 ml of a Cabernet Sauvignon/Merlot red wine containing 12·5% alcohol by volume or 250 ml of a de-alcoholized red wine containing less than 0.5% alcohol by volume" Comment - no information was provided on the method of allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Comment - study was not blinded for participants and personnel

Agewall 2000 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Images were digitally acquired from the videotape and measured in random order by a single observer blinded to the phase of the study and randomization code" Comment - blinding of outcome assessors was probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	“All subjects returned for a second examination within one week” Comment - all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	High risk	Comment - study authors did not report SBP
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	High risk	Comment - study authors did not report DBP .
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SD
Other bias (conflict of interest, industry sponsorship)	Low risk	"This study was supported by grants from the Swedish Medical Research Council, Swedish Medical Society"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Barden 2013

Study characteristics	
Methods	Randomised controlled trial, 3-period open-label cross-over study
Participants	25 men with mean age of 56 years were recruited for the study Inclusion criteria: • Males between 20 and 65 years of age • Alcohol consumption > 30 g/d to < 110 g/d • Non-smoker • Not taking any medication Exclusion criteria:

Barden 2013 *(Continued)*

	• Alcohol consumption < 30 g/d to > 110 g/d, smoker, taking medication • Women were excluded from the study because the protocol required that a relatively high dose of alcohol be consumed in a single session • Smoking within the past 6 months • BMI > 30 kg/m^2 • Chronic liver disease • Cardiovascular disease • Diabetes mellitus • Blood pressure above 160/90 mmHg or treatment with antihypertensive agent • Total cholesterol above 7.5 mmol/L or use of lipid-lowering agents, aspirin, or NSAID
Interventions	• 375 mL of red wine with approximately 14% alcohol content (41 g of alcohol) • Equivalent volume of de-alcoholised red wine with approximately 0.6% alcohol content (DRW) • Water
Outcomes	• Measurement of plasma 20-hydroxyeicosatetraenoic acid • Measurement of plasma epoxyeicosatetraenoic acids and dihyroxyeicosatetraenoic acid metabolites • Measurement of F2-isoprostanes and endothelin-1 • Systolic blood pressure • Diastolic blood pressure • Heart rate
Notes	• Study authors estimated that studying 20 to 25 men would give them at least 80% power to detect a 20% difference in plasma 20-HETE and power to detect a 20% difference in plasma 20-HETE and a 5-mmHg difference in SBP at a significance level of P < 0.05 • The men were asked to maintain their usual drinking, dietary, and exercise habits during the study but to abstain from drinking alcohol for 48 hours before each study visit and from taking any dietary supplements for 2 weeks before and during the study • Washout period was 2 weeks between interventions • We calculated MAP from reported SBP and DBP. SD for MAP had to be imputed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomized using permuted block randomization by a statistician who was not involved with the study to drink a different beverage each day" Comment - method of random sequence generation was not reported but reported baseline characteristics were well matched
Allocation concealment (selection bias)	Unclear risk	"Subjects enrolled after screening and medical examination by research nurse who requests treatment allocation from a statistician not involved in the trial" [from protocol] Comment - method of allocation concealment was unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessors

Barden 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Twenty-four men completed the study; one withdrew because of work commitments" Comment - only 1 participant withdrew from the study and the reason was reported
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP in a figure
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP in a figure
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR in a figure
Other bias (conflict of interest, industry sponsorship)	Low risk	"This work was funded by a project grant from the National Health and Medical Research Council of Australia"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	Low risk	"The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12608000467336"

Bau 2005

Study characteristics	
Methods	Randomised controlled trial, double-blinded, parallel-group assignment
Participants	100 males with mean age of 20.74 ± 2.36 (SD) years (range 18 to 25 years) with no history of cardiovascular disease or medication use and non-smokers Baseline characteristics: • Baseline systolic blood pressure (mean ± SEM) was 115.5 mmHg and diastolic blood pressure (mean ± SEM) was 67.7 mmHg in the placebo group • Baseline systolic blood pressure (mean ± SEM) was 114.2 mmHg and diastolic blood pressure (mean ± SEM) was 64.8 mmHg in the alcohol group • Baseline heart rate (mean ± SEM) was 72.17 ± 1.54 bpm in the placebo group • Baseline heart rate (mean ± SEM) was 72.43 ± 1.59 bpm in the alcohol group
Interventions	• 500 mL placebo beverage containing 2.6 g citric acid, 35.6 g glucose, and distilled water was given to placebo group • 500 mL alcohol beverage containing 2.6 g citric acid, 35.6 g glucose, 60 g of ethanol, and distilled water was given to alcohol group

Bau 2005 *(Continued)*

Outcomes	• Diameter of brachial artery (DBA) • Endothelium-dependent flow-mediated dilation • Endothelium-independent nitoglycerin-mediated dilation • Systolic blood pressure (SBP) • Diastolic blood pressure (DBP) • Heart rate Measurements were made at 10 PM (4 hours after intervention) and at 7 AM (13 hours after intervention)
Notes	• All volunteers were asked to abstain from alcohol and other psychoactive substances 48 hours before the study • Mean arterial pressure (MAP) was not given but can be calculated by using the formula: MAP = 1/3 (SBP - DBP) + DBP; SD was imputed • Adverse events experienced by participants included dizziness and vomiting

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The allocation of groups to either an alcohol containing drink or a similar nonalcoholic beverage was performed with a random seed generator" Comment: adequate randomisation was done and baseline characteristics of groups were well matched
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Investigators and volunteers were blinded to the content of the drink, with or without alcohol" Comment: even though study authors mentioned investigators and volunteers were blind to content of the drink, method of blinding was not mentioned in the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The same sonographer, certified for heart and vascular ultrasound, blind to the control and test groups, evaluated all subjects" Comment: adequate blinding of outcome assessors was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment - all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM in a figure
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SEM in a figure
Selective reporting (reporting bias)	High risk	Comment - study authors did not report MAP

Bau 2005 *(Continued)*

For mean arterial blood pressure (MAP)		
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM
Other bias (conflict of interest, industry sponsorship)	Low risk	"The Instituto Cardiovascular (ICARDIO) and Conselho Nacional de Desenvolvimento Cienti'fico e Tecnolo'gico (CNPq) funded this research"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Bau 2011

Study characteristics	
Methods	Randomised controlled trial, double-blinded, parallel-group assignment
Participants	70 healthy men with mean age of 20.7 ± 2.4 (SD) years (range 18 to 25 years) without cardiovascular disease, not using drugs with cardiovascular effects, and non-smokers were recruited from general population for the study Baseline characteristics: • Baseline mean age was 20.9 ± 2.4 years in the placebo group and 20.6 ± 2.4 years in the alcohol group • Baseline body mass index (BMI) was 23.2 ± 2.2 kg/m² in the placebo group and 22.1 ± 2.0 kg/m² in the alcohol group • Baseline mean blood pressure (MAP) was 87.2 ± 7.8 mmHg in the placebo group and 86.6 ± 9.0 mmHg in the alcohol group • Baseline heart rate (mean ± SD) was 75 ± 10 bpm in the placebo group and 77 ± 11 bpm in the alcohol group
Interventions	• 500 mL placebo beverage containing 2.6 g citric acid, 35.6 g glucose, and distilled water was given to placebo group • 500 mL alcohol beverage containing 2.6 g citric acid, 35.6 g glucose, 60 g of ethanol, and distilled water was given to alcohol group
Outcomes	• Heart rate variability • Standard deviation of all normal R-R intervals (SDNN) - to evaluate vagal modulation to the sinus node • Root mean square of successive difference (RMSSD) - to evaluate vagal modulation to the sinus node • Percentage of pairs of adjacent R-R intervals differing by more than 50 ms (PNN50) - to evaluate vagal modulation to the sinus node Measured during pre-ingestion; 1 to 4 hours after ingestion (high plasma levels of alcohol, with vasodilation and lower blood pressure); 4 to 10 hours after ingestion (vanishing of alcohol); and between 10 and 17 hours after ingestion (after elimination, when there is a late increase in blood pressure)
Notes	• All volunteers were asked to abstain from alcohol and other psychoactive substances 48 hours before the study
Risk of bias	

Bau 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The allocation to the alcohol and control groups was performed with a random seed generator" Comment - baseline data between groups were matched. Adequate randomisation was done
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Investigators and volunteers were blinded to the content of the drink" Comment - even though study authors mentioned investigators, and volunteers were blinded to the content of the drink, method of blinding was not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An investigator blinded in relation to the experimental groups performed the evaluations" Comment - adequate blinding of outcome assessment was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment - all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	High risk	Comment - study authors did not report SBP
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	High risk	Comment - study authors did not report DBP
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SD
Other bias (conflict of interest, industry sponsorship)	Low risk	"Grants from the Instituto Cardiovascular (ICARDIO) and Conselho Nacional de Desenvolvimento Cientı´fico e Tecnolo´gico (CNPq) funded this research. Disclosures: none"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Buckman 2015

Study characteristics	
Methods	Randomised controlled trial, parallel-group assignment, open-label study
Participants	72 healthy participants with average age of 21.7 years (SD = 0.9). Among participants, 44% were female Exclusion criteria: • Younger than 21 years of age • Reported consuming fewer than 4 drinks (3 drinks for women) twice per month in the past year, or • Were more than 20% overweight or underweight from the ideal for gender, height, and body frame based on the Metropolitan Life Height–Weight Table • Regular (greater than monthly) drug use • Self-report of current learning disability • Lifetime history of bipolar disorder or psychosis diagnosis • Substance use treatment in the past year • Biological mother with heavy substance use during pregnancy • For women, pregnancy
Interventions	• 95% ethanol with mixer (orange, cranberry, and lime juice) calculated based on body weight: 0.90 mL/kg for men, 0.78 mL/kg for women • Physiologically inactive dose of alcohol (100 µL EtOH float per each cup) with mixer • Placebo (100% mixer, no alcohol) Each beverage was divided into 3 equal drinks, and participants were instructed to consume each beverage evenly over a 5-minute period (total drinking time = 15 minutes)
Outcomes	• Variability in cardiovascular function: heart rate variability (HRV), high-frequency HRV, low-frequency HRV, stroke volume variability (mL), pulse transit variability (ms), systolic blood pressure variability (mmHg) • Average cardiovascular activity: heart rate (bpm), stroke volume (mL), pulse transit time (ms), systolic blood pressure (mmHg), mean arterial blood pressure (mmHg) • Sensitivities of cardiovascular function: heart rate baroreflex sensitivity, stroke volume baroreflex sensitivity, vascular tone baroreflex sensitivity
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	“Participants were randomly assigned to the alcohol, placebo, or no-alcohol beverage group” "Upon arrival in the laboratory, weight, height, pregnancy status, and a zero blood alcohol concentration (BAC) were confirmed and participants were randomly assigned to the alcohol, placebo, or no-alcohol beverage group, as described below" "Table 1 shows that groups were not statistically different in terms of demographics, family history of alcohol dependence, alcohol use, and mood" Comment - adequate randomisation was probably done and baseline characteristics between groups were well matched
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described

Buckman 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	"Participants in the alcohol group (n = 24) were told that they would receive some amount of alcohol and were given mixer (orange, cranberry, and lime juice) with an active ethanol…" "Participants in the placebo group (n = 24) were told that they would be given some amount of alcohol and received mixer with a physiologically inactive dose of alcohol…" "The no-alcohol control group (n = 24) were told that they would not be given alcohol and received 100% mixer" Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment - all participants were included in the final analysis (additional information from study author)
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SD
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	High risk	Comment - study authors did not report DBP
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - study authors reported MAP and SD
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SD
Other bias (conflict of interest, industry sponsorship)	Low risk	"This study was funded with the support of K01AA017473, K02AA00325, K24AA021778, R21AA020367, and HHSN275201000003C"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Chen 1986

Study characteristics	
Methods	Randomised controlled trial, parallel-group assignment, open-label study
Participants	20 college students, both male and female, between the ages of 19 and 32 years, participated in the study

Chen 1986 *(Continued)*

	Inclusion criteria: • Non-smoker • Non-alcoholic or with no drinking problem • No blood pressure problem • Good general health
Interventions	• Sufficient quantities of beer or wine to achieve a blood level of 0.05% • No alcohol
Outcomes	• Heart rate • Systolic blood pressure • Diastolic blood pressure • Respiratory rate • Subjective ratings of anxiety level
Notes	• All tests were conducted in a group setting in the laboratory. Alcohol and control groups were tested separately at about the same time of day to control possible variation due to change in biological rhythms

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"After the initial screening, subjects were randomly assigned to either an alcohol group or a control group" Comment - method of randomisation was not reported; baseline characteristics of groups were not reported either
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	"Two subjects in the alcohol group dropped from the study for unknown reasons. Data analyses were based on 8 subjects in the alcohol group and 10 subjects in the control group" Comment - 2 participants withdrew from alcohol-receiving group; reasons for withdrawal are not mentioned
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP along with standard deviation (SD)
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP along with standard deviation (SD)

Chen 1986 *(Continued)*

Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR along with standard deviation (SD)
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not report any conflicts of interest or sponsorship
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Cheyne 2004

Study characteristics	
Methods	Randomised controlled trial, double-blinded, cross-over design
Participants	17 participants (14 male, 3 female) with mean age of 35 years (range 21 to 46 years), with type 1 diabetes, HbA1c 8.1% (1.4%) [mean (SD)], and duration of diabetes 19 years (12 years) were studied. All were drivers and drank alcohol (between 1 and 14 units per week). They did not have a history of alcoholism or drug abuse and were not taking any other medication apart from insulin
Interventions	• 0.35 mg/kg of alcohol (vodka and sugar-free orange squash) • Placebo (similar volume of sugar-free orange squash only)
Outcomes	• Heart rate • Blood pressure • Cognitive function • Hazard perception test • Blood glucose and alcohol level
Notes	• All studies were done in the Diabetes and Endocrine Centre at the Royal Bournemouth Hospital • Washout period between sessions was 2 weeks • 16 patients in the study had 80% power to detect effect sizes of 0.75 within-subject standard deviations for all outcomes

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Subjects participated in four studies in a random order: (A) Euglycaemia (4.5 mmol/l) with placebo (B) Euglycaemia (4.5 mmol/l) with alcohol (C) Hypoglycaemia (2.8 mmol/l) with placebo (D) Hypoglycaemia (2.8 mmol/l) with alcohol"

Cheyne 2004 *(Continued)*

		"(order determined using computer-generated random selection of 4 × 4 Latin squares [15] and concealed using opaque envelopes" Comment - adequate randomisation was done
Allocation concealment (selection bias)	Low risk	"(order determined using computer-generated random selection of 4 × 4 Latin squares [15] and concealed using opaque envelopes" Comment - adequate allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Subjects were blinded to the content of the drink and the prevailing blood glucose level, although some reported that they were able to detect alcohol by taste" Comment - blinding of participants was not successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Research assistant supervising cognitive function tests was blinded to both contents of the drink and blood glucose level Comment - adequate blinding of outcome assessment was done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - study authors did not report anything about patient withdrawal or whether all participants completed all 4 sessions
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP, along with the standard deviation (SD)
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP along with the standard deviation (SD)
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR along with the standard deviation (SD)
Other bias (conflict of interest, industry sponsorship)	Low risk	"This study was supported by a grant from the South-west NHS R&D executive"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Dai 2002

Study characteristics

Dai 2002 *(Continued)*

Methods	Randomised controlled trial, double-blinded, cross-over design
Participants	20 participants with high risk and 20 participants with low risk of alcoholism (total 40 participants) were included in the study. All participants were men and were between 19 and 25 years old Inclusion criteria: not reported Exclusion criteria: • Michigan Alcoholism Screening Test score ≥ 10 (Selzer 1971), as well as presence of alcohol dependence or abuse diagnosis (DSM-IV) (American Psychiatric Association 1994) • Medical problems, such as liver or kidney problems, diabetes, hypertension, or other chronic disease • Mental health problems, such as depression or schizophrenia • Use of prescribed psychotropic drugs • Use of drugs of abuse other than alcohol, such as cocaine and cannabis • Smoking of more than 10 cigarettes per day • Female individuals were not included in these studies because of the complexity of controlling for phases of the reproductive cycle and use of various contraceptive medications • Individuals whose mother was, or had previously been, an alcoholic were excluded from the study to avoid including those exposed to ethanol during foetal life
Interventions	• Ethanol (0.50 g/kg) • Placebo drink (1 part de-gassed tonic water and 2 parts unsweetened orange juice) Beverage was consumed as a single drink within 5 minutes
Outcomes	• Heart rate • Systolic blood pressure • Diastolic blood pressure • Estimation of blood alcohol level (BAC) • Estimation of plasma β-endorphin levels HR, SBP, and DBP measurements were taken at baseline and at 5, 20, 35, 50, 65, 95, 125, 155, 185, 215, and 245 minutes after ingestion of the drink
Notes	All participants were requested to abstain from alcohol for 48 hours before each testing session

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Each subject participated in four testing sessions administered in a random order; the sessions were double-blinded with respect to the ingestion of the alcohol or placebo drink” “The HR and LR subjects were matched for age, body weight, education, smoking behavior, and drinking behavior, such as age at onset and quantity and frequency of drinking (Table 1)” Comment - method of randomisation was not described but baseline characteristics were matched
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	"The lips of the glass were dipped in alcohol to give it the smell and taste of alcohol. Subjects initially could not distinguish between the placebo and alco-

Dai 2002 *(Continued)*

All outcomes		hol drinks. However, in the absence of the pharmacological effects of ethanol, some subjects did suspect that they had consumed a placebo drink" Comment - adequate attempt was made to blind participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All measurements of the cardiovascular function were taken manually, while the subjects reclined in bed, by a research nurse blinded to the treatment and risk type of the subjects" Comment - adequate blinding of outcome assessment was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	"A total 20 HR and 20 LR subjects completed the study" Comment - all 40 participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP in a figure
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP in a figure
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR in a figure
Other bias (conflict of interest, industry sponsorship)	Low risk	Comment - study was supported by the Canadian Institutes on Health Research
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Dumont 2010

Study characteristics	
Methods	Randomised controlled trial, 4-way, double-blind, cross-over design
Participants	16 healthy volunteers (9 male and 7 female) with mean age (SD) of 22.1 (2.9) years (range 18 to 29) Inclusion criteria: • Regular users of ecstasy (at least 8 exposures in the last 2 years) and alcohol (at least 1 exposure per week) Exclusion criteria:

Dumont 2010 *(Continued)*

	• Pregnancy • History of psychiatric illness • Use of over-the-counter medication within 2 months before study start • (History of) treatment for addiction problems • (Familial or personal history of) schizophrenia • Excessive smoking (> 10 cigarettes/d) • Orthostatic dysregulation
Interventions	• Ethanol infusion (target blood alcohol concentration of 0.6%) • Placebo infusion (glucose 5%) as placebo for ethanol infusion • 100 mg MDMA capsule • Placebo for MDMA
Outcomes	Cardiovascular function assessed by: • Heart rate • Systolic blood pressure • Diastolic blood pressure Plasma concentration of: • Antidiuretic hormone (ADH) • Sodium • Norepinephrine (NE) • Epinephrine (E)
Notes	• Washout was 7 days between treatments • Light breakfast was offered • A 30-minute lunch break was scheduled 210 minutes after drug administration • Drug administration was scheduled at 10:30 hours and ethanol infusion was started at 11:00 hours • Outcomes were assessed before administration and at 30, 90, 150, 240, 300, and 360 minutes after administration • Alcohol clamp was targeted at 0.6‰ - the equivalent of approximately 2 to 3 alcoholic beverages • Drug use was not allowed 14 days before the first study day until study completion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Sixteen volunteers were randomly assigned to one of the four treatment sequences” Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment - method of blinding was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The operator of the breath alcoholmeter and the ethanol infusion pump was unblinded for alcohol treatment, but did not communicate with the study team or the subject about the results at any stage during the trial. A sham procedure including a mock-spreadsheet was used on ethanol-placebo-occasions"

Dumont 2010 *(Continued)*

		Comment - it is not mentioned whether heart rate and blood pressure were measured in a blinded fashion
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant had a mild adverse reaction (local vascular reaction) to the ethanol infusion, and 1 participant did not refrain from drug use; both (1 male and 1 female) were excluded from further participation and results obtained from these individuals were not included in the final data analysis Comment - reasons for exclusion of 2 participants were reported and balanced across groups, so missing data should not affect the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	High risk	Comment - study authors did not provide the before and after measure of SBP. They mentioned that the change was not significant
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	High risk	Comment - study authors did not provide the before and after measure of DBP. They mentioned that the change was not significant
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - study authors reported MAP in a figure
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR in a figure
Other bias (conflict of interest, industry sponsorship)	Low risk	This research was supported by a grant from ZonMW (31000062), the Netherlands, and complies with current laws
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Fantin 2016

Study characteristics	
Methods	Randomised controlled trial, open-label with cross-over design
Participants	18 healthy adults (12 male and 6 female) with mean age 34.2 years (range 25 to 53 years) Exclusion criteria: • Individuals > 55 years old • Individuals with hypertension or diabetes, any arrhythmia, heart failure, valvular heart disease, malignancy, renal failure, body mass index > 30 kg/m^2, or on hormone replacement therapy
Interventions	250 mL of red wine (12% of ethanol)
Outcomes	Heart rate, BP, and arterial stiffness, as assessed by QKD

Fantin 2016 *(Continued)*

Notes	• Participants were asked not to drink for 24 hours before 24-hour ambulatory readings of the first day • Investigators did not record which type of food they ate during the study day • None of the participants ingested caffeine during study days • None of the participants indulged in binge drinking during the study • None of the participants was involved in intense physical activity during the study • Alcohol was ingested between 1830 hours and 0430 hours • We calculated MAP from SBP and DBP • Readings were taken approximately every half hour with an ambulatory BP monitor

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The subjects received the two days in random order" "The subjects were randomly allocated to either consuming alcohol on the first day (control day second) or the control day first" Comment - method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - participants and personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Our study sample was composed of 21 healthy adult volunteer men and women. 3 of them decided not to go on with the study so the final sample was composed of 18 subjects" Comment - study included only participants who finished the study, hence participant withdrawal did not affect results. 18 participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - SBP data with SD were reported
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - DBP data with SD were reported
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - MAP data were not reported
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - HR data with SD were reported

Fantin 2016 *(Continued)*

Other bias (conflict of interest, industry sponsorship)	Low risk	"The authors declare no conflict of interest"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Fazio 2004

Study characteristics	
Methods	Randomised controlled trial, open-label with cross-over design
Participants	10 young healthy and normotensive male volunteers with mean age of 22 ±2.1 (SD) years (range 20 to 25 years)
Interventions	• 95% ethanol infusion via arm vein (7.5 mg/kg/min in 250 mL saline) • 95% ethanol, 0.3 g/kg in 250 mL water, orally, within 5 minutes • 250 mL saline infusion alone in 40 minutes (6.25 mL/min)
Outcomes	• Heart rate • Mean blood pressure • Cardiac index • Total peripheral vascular resistance • Changes in diameter, mean blood velocity, and mean blood flow of carotid artery in diameter • Changes in diameter, mean blood velocity, and mean blood flow of branchial artery in diameter
Notes	• Participants rested quietly in recumbent position for 30 minutes to allow blood pressure and heart rate to stabilise before measurement of baseline haemodynamic variables

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"In random order the subjects drank 95% ethanol, 0.3 g/kg in 250 mL water, in the sitting position in 5 minutes or had 95% ethanol…." Comment - method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - participants and personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - because this study was open-label, outcome measurement was likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis

Fazio 2004 *(Continued)*
All outcomes

Selective reporting (reporting bias) For systolic blood pressure (SBP)	High risk	Comment - SBP data with SD were not reported
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	High risk	Comment - DBP data with SD were not reported
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - MAP data with SD were reported
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - HR data with SD were reported
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not report any funding source or conflict of interest
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Foppa 2002

Study characteristics	
Methods	Randomised controlled trial, open-label with cross-over design
Participants	13 hypertensive and centrally obese individuals (8 postmenopausal women and 5 men) Inclusion criteria: • Study participants were required to have systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, on at least 2 separate measurements, or had to be taking antihypertensive drugs • Central obesity was defined for this specific study as one of the following: body mass index (BMI) > 30 kg/m^2; BMI > 27.3 kg/m^2 with waist-hip ratio > 0.95 for women; or BMI > 27.8 kg/m^2 with waist-hip ratio > 1.05 for men • Men were between 35 and 65 years of age; women were postmenopausal (last menses more than 1 year ago) and were younger than 66 Exclusion criteria: • History of heavy alcohol ingestion, defined as average ethanol intake > 30 g/d • Diagnosed diabetes mellitus; symptomatic ischaemic heart disease; evidence of major target organ damage; or presence of disease or use of a drug that could adversely influence blood pressure or metabolic control
Interventions	• 250 mL of red wine (23 g ethanol) • Placebo equivalent (200 mL of water and 50 mL of grape juice)

Foppa 2002 *(Continued)*

Outcomes	• Systolic blood pressure • Diastolic blood pressure • Mean blood pressure • Heart rate Measured at the following time intervals: postprandial (3 hours from intervention), daytime (1200 hours to 2200 hours), nighttime (2200 hours to 0700 hours), and overall (19-hour interval, from intervention at 1200 hours to 0700 hours, Day 2)
Notes	• Hospital settings • Participants were instructed not to change diet, sleep, physical activity, or smoking habits across the entire study. They were also instructed to fast for at least 12 hours, abstain from alcohol intake for 36 hours, and not take antihypertensive drugs from 3 days before each study period • Washout period was 1 to 3 weeks between experimental periods • Wine and control solutions were administered at 1200 hours together with a standardised meal over a 15-minute interval. The meal was composed essentially of carbohydrates (pasta, tomato sauce, and a jelly dessert), with total energy content of 650 kcal • Participants were allowed to take their pre-study antihypertensives during the washout period and were told to stop them 3 days before the study day

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"the randomization order in this crossover randomized clinical trial was done with sealed randomized envelopes in blocks of 8 (envelopes were prepared by a third person unaware of research objectives or protocol)" [information was provided by study author] Comment - adequate random sequence generation was done
Allocation concealment (selection bias)	Low risk	"the randomization order in this crossover randomized clinical trial was done with sealed randomized envelopes in blocks of 8 (envelopes were prepared by a third person unaware of research objectives or protocol)" [information was provided by study author] Comment - adequate allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - participants and personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment - all 13 participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP with SD in a figure
Selective reporting (reporting bias)	Low risk	Comment - study authors reported DBP with SD in a figure

Foppa 2002 *(Continued)*

For diastolic blood pressure (DBP)		
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - study authors reported MAP with SD
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR with SD in a figure
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not report any funding source or conflict of interest
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Hering 2011

Study characteristics	
Methods	Randomised controlled trial, open-label with cross-over design
Participants	Total 24 participants; 13 patients (8 men and 5 women) with essential hypertension and 11 normotensive controls (6 men and 5 women) matched for sex, age (44 ± 2 vs 43 ± 2 years, respectively; mean ± SEM), and BMI (29 ± 1 vs 28 ± 1 kg/m^2, respectively) Inclusion criteria: • Hypertensive patients with stage 1 and 2 hypertension who were newly diagnosed, never treated for hypertension, and free of any other disease • All participants consumed alcoholic beverages socially (between 100 and 200 g of alcohol a week, with median of 150 g consumed in both groups) Exclusion criteria: • Patients with white-coat hypertension and controls with masked hypertension
Interventions	• Alcohol (1.0 g/kg body weight, diluted in 500 mL low caloric orange juice) or • Vehicle (500 mL of low caloric orange juice) Administered over a period of 20 minutes
Outcomes	• Heart rate • Systolic blood pressure • Diastolic blood pressure • Muscle sympathetic nerve activity
Notes	• Standard light breakfast was provided before the experiment • All participants were asked to abstain from alcohol for at least 36 hours • 10-minute recordings were performed 10 minutes after completion of drinking either alcohol or placebo

Hering 2011 *(Continued)*

- We calculated MAP from reported SBP and DBP. SD was imputed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The study design was randomized and placebo-controlled with two experimental sessions (an alcohol session and a vehicle session). The sessions were performed at the same time of day on two separate days in random order" "The assignment of subjects to either begin the study protocol with an alcohol session or vehicle session was performed by a random allocation using the randomized computer generated number table" [information was given by study authors] Comment - adequate random sequence generation was done and baseline characteristics were matched
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - participants and personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP with SEM
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP with SEM
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR with SEM
Other bias (conflict of interest, industry sponsorship)	Low risk	"These studies were supported by NIH HL61560 and NIH FIRCA Award R03 TW0 1148. The authors are also supported by European Union LSHM-CT-2006-037093 InGenious grant (K.N. and W.K.), and by Foundation for Polish Science TEAM/2008-2/5 (K.N. and W.K.) and MISTRZ 8/2008 (K.N. and D.H.) grants"

Hering 2011 *(Continued)*

		"There are no conflicts of interest"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Karatzi 2005

Study characteristics	
Methods	Randomised controlled trial, double-blinded, cross-over design
Participants	15 male participants with coronary artery disease with mean age of 52.4 ± 9.7 (SD) years and BMI of 28.3 ± 1.8 kg/m^2 Inclusion criteria: • Coronary angiography was performed within the past 6 months and no revascularisation procedure was carried out in the past 3 months Exclusion criteria: • Presence of diabetes mellitus, obesity, or any liver, kidney, or endocrine disease, and administration of antioxidant vitamin supplementation
Interventions	• 250 mL of regular (12% ethanol, Grand Reserve 1996, Boutaris, Greece) or • 250 mL of de-alcoholised red wine (< 1% ethanol)
Outcomes	• Central and peripheral blood pressures (BPs) • Arterial stiffness • Heart rate Assessed at fast and at 30, 60, and 90 minutes postprandially
Notes	• Sample size of 15 participants was estimated as efficient (80% power) to demonstrate a change by 6% in augmentation index (AIx) (α = 0.05 and β = 0.20; 2-tailed test) • All participants were receiving nitrates, β-blockers, antiplatelets. Nine of them (60%) were taking angiotensin-converting enzyme inhibitors, and 2 (13.3%) calcium channel blockers. Furthermore, all participants were ex-smokers, and their alcohol use complied with recommendations (20 to 30 g alcohol/d)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomly allocated to drink either a glass of 250 mL of red wine or 250 mL of dealcoholized red wine" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Unclear risk	“duo–trio tests* and a hedonic scale were used to test whether de-alcoholised red wine could be well accepted by the subjects who would consume it, and whether it could be recognized compared with regular red wine”

Karatzi 2005 *(Continued)*

All outcomes		"results from the duo–trio tests and the hedonic scale analysis showed that the subjects could not distinguish the two wines, as they could not correctly recognize the presence or absence of alcohol" Comment - it is not clear whether personnel who administered the intervention were blinded as well
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment - it is not mentioned whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP with SEM
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP with SEM
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - study authors reported MAP with SEM
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR with SEM
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not report any funding source or conflict of interest
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Karatzi 2013

Study characteristics	
Methods	Randomised controlled trial, single-blinded, cross-over design
Participants	17 healthy, non-smoking male volunteers with a mean age of 28.5 ± 5.2 years and body mass index (BMI) of 24.4 ± 2.5 kg/m^2 Exclusion criteria: • Medical history of coronary artery disease, diabetes mellitus, or liver or endocrine disease • Smoking, alcohol consumption greater than recommended amount (20 to 30 gr alcohol/d), vigorous exercise, antioxidant vitamin supplementation

Karatzi 2013 *(Continued)*

	• Dieting at the time of the study
Interventions	• 400 mL of beer and 400 mL of water (~ 20 g of ethanol and ~ 48 mg polyphenol) • 800 mL of de-alcoholised beer (same quantity of polyphenols) • 67 mL of vodka and 733 mL of water (same amount of alcohol) Consumed within 15 minutes
Outcomes	• Endothelial function (brachial flow-mediated dilatation) • Aortic and brachial pressure • Aortic stiffness (pulse wave velocity, pressure wave reflections (AIx)) Assessed at fast and at 1 and 2 hours postprandially
Notes	• All vascular and haemodynamic tests were performed at the Cardiovascular Research Laboratory (Laiko Hospital) in the morning hours (at 8:00) and after 10 to 12 hours of fast and absence of alcohol, coffee, and caffeinated drinks since noon of the previous day • Washout period was at least 1 week • Test drinks were accompanied with a sandwich (2 slices of white bread, 1 slice of turkey, and 1 slice of low-fat cheese) • The above-mentioned drinks were matched for their antioxidant and alcohol content, namely, 400 mL of beer had the same antioxidant concentration as 800 mL of de-alcoholised beer (~ 48 mg polyphenols), and 400 mL of beer had the same alcohol concentration as 67 mL of vodka (~ 20 g of ethanol) • All volunteers were instructed to avoid significant changes in their physical activity and in their diet between the 3 visits • They were also advised to consume the same quality and quantity of food 1 day before the study days began

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"all volunteers consumed in a randomized order either a) 400 ml of beer & 400 ml water, b) 800 ml of dealcoholized beer (same amount of polyphenols), or c) 67 ml of vodka & 733 ml water" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“The same trained observer who was blinded for the type of intervention performed all measurements" Comment - blinding of outcome assessors was probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	“Data from 16 subjects were available for the final analysis due to missing values related to poor quality of vascular recordings in at least one of the visits” Comment - reasons for exclusion of a participant were reported and balanced across groups, so missing data should not affect the final analysis
Selective reporting (reporting bias)	High risk	Comment - study authors did not report SBP

Karatzi 2013 *(Continued)*

For systolic blood pressure (SBP)		
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	High risk	Comment - study authors did not report DBP
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - study authors reported MAP with 95% confidence interval
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR with 95% confidence interval
Other bias (conflict of interest, industry sponsorship)	Low risk	"The authors declare that they have no conflict of interest"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Kawano 1992

Study characteristics	
Methods	Randomised controlled trial, open-label, cross-over design
Participants	16 Japanese men (22 to 70 years old) with essential hypertension. Mean age was 55.2 ± 3.3 years (mean ± SEM)
Interventions	• 1 mL/kg ethanol (vodka) • Non-alcoholic beverage (lime juice and water) Ingested at dinner
Outcomes	Ambulatory blood pressure and heart rate were measured every 30 minutes until noon the next day
Notes	• Alcohol was forbidden for at least 7 days before the study • Participants were asked to discontinue their antihypertensive medication for at least 7 days before the study • All participants were admitted to the National Cardiovascular Center Hospital, where they consumed a standard daily diet of 6300 kJ (1500 kcal) that contained 7 to 9 g NaCl • All participants were habitual drinkers • All participants were diagnosed as having mild to moderate essential hypertension (average diastolic blood pressure 90 to 114 mmHg) • No participant had a serious cardiac, neurological, or hepatic disorder • Interventions were given at dinner • All participants were admitted to the National Cardiovascular Center Hospital, where they consumed a standard daily diet of 6300 kJ (1500 kcal) that contained 7 to 9 g NaCl • The 2 study periods were separated by a rest day

Kawano 1992 *(Continued)*

- We calculated MAP from reported SBP and DBP. SD for MAP had to be imputed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"the order of alcohol intake day and control day was randomized to minimize the influences of various factors including the order effect" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Data for three patients were excluded because the ambulatory recordings were not available for the entire period" Comment - reasons for exclusion of 3 participants were reported and balanced across groups, so missing data should not affect the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP with SD
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP with SD
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR with SD
Other bias (conflict of interest, industry sponsorship)	Low risk	"Supported by Research Grant for Cardiovascular Diseases 63C-2 from the Ministry of Health and Welfare"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Kawano 2000

Study characteristics	
Methods	Randomised controlled trial, open-label, cross-over design
Participants	10 Japanese hypertensive patients with mean age ± SEM of 54 ± 3 years and body weight 70 ± 2 kg Inclusion criteria: • Mild essential hypertension
Interventions	• 1 mL/kg of alcohol (vodka with lime juice and water) or • Isocaloric control drink (Calorie Mate, Otsuka Pharmaceutical Co., Tokushima, Japan) Consumed within 60 minutes • Prazosin 1 mg, 3 times daily plus alcohol
Outcomes	• Systolic blood pressure • Diastolic blood pressure • Heart rate • Serum electrolyte level BP and HR were measured every 30 minutes for 24 hours
Notes	• Light meal was provided with interventions • All participants had average daily alcohol consumption of 30 to 120 mL (mean ± SEM: 72 ± 13 mL) • Antihypertensive medication was discontinued for ≥7 days before the study • We calculated MAP from reported SBP and DBP. SD for MAP had to be imputed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The order of the alcohol and control days was randomized" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP with SEM

Kawano 2000 *(Continued)*

Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP with SEM
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR with SEM
Other bias (conflict of interest, industry sponsorship)	Low risk	"This study was supported by a Research Grant for Cardiovascular Diseases 5A-2 from the Ministry of Health and Welfare, and a grant from Takeda Medical Research Foundation"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Koenig 1997

Study characteristics	
Methods	Randomised controlled trial, open-label, cross-over design
Participants	15 males between the ages of 20 and 35 years (average gross height 184 cm, weight 76 kg) were enrolled in the study Exclusion criteria: • Patients with acute or chronic disease
Interventions	• 10 mL/kg body weight of Kölsch (beer), or • Same amount of Kolschbier brewing water was chosen as placebo Consumed within 30 minutes
Outcomes	• Systolic blood pressure • Diastolic blood pressure • Serum electrolyte level Measured at baseline and at 2 and 3 hours after consumption
Notes	• Washout period was 14 days between interventions • Participants were told to abstain from alcohol for 5 days before the study

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment - method of randomisation was not described

Koenig 1997 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP with SD in a figure
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP with SD in a figure
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	High risk	Comment - study authors did not report HR
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not mention any funding source or declare any conflict of interest
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Kojima 1993

Study characteristics	
Methods	Randomised controlled trial, open-label, cross-over design
Participants	21 men with essential hypertension and mean (SD) age of 56.5 (11.8) were enrolled in the study Exclusion criteria: • Individuals with serious heart, liver, or kidney disease
Interventions	• Alcohol in the form of vodka made up to 500 mL with lime juices

Kojima 1993 *(Continued)*

	• 500 mL lime juice made isocaloric by addition of a candy (Caloriemate, Otsuka Pharmaceutical Ltd., Japan)
Outcomes	• Heart rate • Systolic blood pressure • Diastolic blood pressure Measured 30 minutes before and 2 hours after consumption
Notes	• Washout period: 2 days • All participants were admitted to the National Cardiovascular Center Hospital and ate a standard daily diet of 6300 kJ containing 7 to 9 g salt • All antihypertensives were discontinued at least 7 days before the study • Drinks were given with supper (1700 to 1730 hours) to mimic the usual drinking pattern

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“with a randomized, balanced crossover design, the effects of alcohol in the form of vodka made up to 500 ml with lime juice, were compared with a control drink..” Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Although serum insulin was measured in only 20 patients, the other parameters were measured in all 21 patients" Comment - all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SEM
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - study authors reported MAP and SEM
Selective reporting (reporting bias)	Low risk	Comment - study authors reported HR and SEM

Kojima 1993 *(Continued)*
For heart rate (HR)

Other bias (conflict of interest, industry sponsorship)	Low risk	"This study was supported in part by Research Grants for Cardiovascular Disease (63-2C and 2C-3) from the ministry of health and welfare"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Mahmud 2002

Study characteristics	
Methods	Randomised controlled trial, double-blinded, cross-over design
Participants	8 healthy normotensive individuals (3 men and 5 women) between the ages of 21 and 40 years with mean ± SEM body weight of 70 ± 3.9 kg
Interventions	• 500 mL of red wine (0.8 g/kg ethanol) or • 500 mL of red wine without alcohol Consumed within 10 minutes
Outcomes	• Brachial and aortic blood pressure • Heart rate • Pulse wave Measured at baseline and at 30, 60, and 90 minutes after ingestion of either drink
Notes	• Participants were not taking any medications or vitamin supplements • Participants had an average alcohol intake of 10 ± 3.8 units/week • Participants were asked to abstain from all caffeine-containing beverages in the 12 hours before each visit, as well as alcohol in the 24 hours before the visit • Washout period was 1 week between the 2 visits • We calculated MAP from reported SBP and DBP. SD for the MAP had to be imputed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Each participant, studied while fasting, consumed 500 mL of red wine (0.8 g/kg ethanol) or 500 mL of red wine without alcohol within 10 minutes in a double-blind, randomised, cross-over fashion Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment - method of blinding of participants and personnel was not mentioned

Mahmud 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment - method of blinding of outcome assessors was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment - all participants were included in the final analysis according to Figure 1
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SEM
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP and SEM
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not mention any funding source nor declare any conflict of interest
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Maufrais 2017

Study characteristics	
Methods	Randomised controlled trial, open-label, cross-over design
Participants	24 healthy young individuals (12 men, 12 women) of European descent with mean ± SD age of 23.3 ± 2.2 years and weight 62.9 ± 10.1 kg Exclusion criteria: • Participants with a body mass index > 30 kg/m^2, competition athletes, and individuals with a daily exercise workload exceeding 60 minutes per day
Interventions	Participants ingested 1 of the following 4 drinks at a temperature of around 10°C (at a convenient pace over 5 minutes): • 390 mL distilled water + 10 mL lemon juice • 48 g sucrose + 10 mL lemon juice, diluted in distilled water up to a total volume of 400 mL • Vodka (40% alcohol per volume, given at 1.28 mL/kg of body weight, providing 0.4 g alcohol/kg) + 10 mL lemon juice, diluted in distilled water up to 400 mL

Maufrais 2017 *(Continued)*

	• 48 g sucrose + 40% vodka (at 1.28 mL/kg) + 10 mL lemon juice, diluted in distilled water up to 400 mL
Outcomes	• Heart rate • Mean blood pressure • Skin temperature • Stroke volume • Cardiac output • Total peripheral resistance Measured before drinking and at 15, 30, 60, 90, and 120 minutes post drinking
Notes	• None of the participants had any disease or were taking any medication affecting cardiovascular or autonomic regulation • All participants were requested to avoid alcohol or caffeine for at least 24 hours before the test • A light standardised breakfast provided by investigators, consisting of 1 mini-pack of 33 cl of commercial light ice tea (33 kcal, 8 g carbohydrates/6.6 g sugar) and 2 cereal bars (total of 150 kcal, 39 g carbohydrates/12 g sugar), to avoid that consumption of alcohol in the same morning was done on an empty stomach • Study authors chose type I error (α) of 0.05 and desired power (1-β) of 0.80, suggesting that a total of 12 participants per gender would be required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random sequence generator (http://www.random.org/sequences/) where the session order was determined for 24 test subjects before the study started"
Allocation concealment (selection bias)	Unclear risk	"The test subjects were not allowed to know the order of their sessions in advance" Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	High risk	Comment - study authors did not report SBP
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	High risk	Comment - study authors did not report DBP
Selective reporting (reporting bias)	Low risk	Comment - study authors reported MAP and SEM

Maufrais 2017 *(Continued)*

For mean arterial blood pressure (MAP)		
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM
Other bias (conflict of interest, industry sponsorship)	Low risk	"The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest" "This work was supported by the Swiss Foundation for Alcohol Research (project 276) and in part by the Swiss National Science Foundation"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Maule 1993

Study characteristics	
Methods	Randomised controlled trial, single-blind, cross-over design
Participants	10 healthy individuals (6 male, 4 female) with mean age of 31 (range 22 to 51) and mean weight of 68.1 kg were included in the study
Interventions	• 40% vodka diluted in sugar-free orange juice with aspartame 0.8 g/100 mL (dose: 0.5 g/kg body weight), or • Placebo consisting of sugar-free orange juice with aspartame 0.8 g/100 mL Consumed within 10 minutes
Outcomes	• Systolic blood pressure • Diastolic blood pressure • Mean arterial blood pressure • Heart rate • Total peripheral vascular resistance • Skin temperature • Digital skin blood flow Blood pressure and heart rate were measured at baseline and every 5 minutes until the 45th minute
Notes	• All participants were off medication and had normal liver function tests • Participants had alcohol consumption < 80 g per week • Alcoholic drinks were not allowed 3 days before the study • Participants refrained from smoking and drinking caffeinated beverages from midnight before the study • Participants were studied after an overnight fast

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Maule 1993 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"subjects were then randomized to receive a drink of either alcohol or placebo which was ingested with a straw over 10 mins in supine position" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment - it is not clear who was blinded or how blinding was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment - it is not clear who was blinded or how blinding was achieved
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SEM
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - study authors reported MAP and SEM
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not report any conflict of interest nor sponsorship
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Narkiewicz 2000

Study characteristics	
Methods	Randomised controlled trial, double-blind, cross-over design

Narkiewicz 2000 *(Continued)*

Participants	19 healthy young volunteers (18 men and 1 women) with mean age ± SD of 26 ± 2 years participated in the study
Interventions	• Alcohol (1.0 g/kg body weight, diluted in 400 mL of water), or • Placebo (400 mL water) Consumed over a 30-minute period
Outcomes	• Lower-body negative pressure • Systolic blood pressure • Diastolic blood pressure • Mean arterial pressure • Heart rate
Notes	• None was taking any medications • All participants were social drinkers only and had abstained from alcohol for a minimum of 48 hours before the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Measurements were obtained by use of a randomized, double-blind, placebo-controlled design with 2 experimental sessions, a placebo session and an alcohol session" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A flavoring (Crystal Light) was added to these solutions to prevent the subjects from distinguishing alcohol from placebo" Comment - blinding of participants was probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Studies were analyzed by investigators blinded to session (alcohol or placebo)" Comment - blinding of outcome assessors was probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Vasovagal responses or discomfort during LBNP in 5 subjects resulted in completion of studies examining the effects of both alcohol and placebo in only 14 subjects (13 men, 1 woman; mean age, 26±2 years)" Comment - reasons for exclusion of participants were reported and balanced across groups, so missing data should not affect the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SEM

Narkiewicz 2000 *(Continued)*

Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - study authors reported MAP and SEM
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM
Other bias (conflict of interest, industry sponsorship)	Low risk	"Dr. Narkiewicz, a visiting research scientist from the Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland, was a recipient of an International Research John E. Fogarty Fellowship (NIH 3F05 TW05200) and a Perkins Memorial Award from the American Physiological Society. Dr. Somers is an Established Investigator of the AHA and a Sleep Academic Awardee of the NIH. Other support includes HL61560 and HL65176 (NIH). We thank Diane Davison, RN, MA, for technical assistance"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Nishiwaki 2017

Study characteristics	
Methods	Randomised controlled trial, single-blind, cross-over design
Participants	11 healthy young men with mean age ± SD of 21.1 ± 0.2 years, body weight 62.6 ± 2.6 kg
Interventions	• 200 mL of beer • 350 mL of beer • 200 mL of alcohol-free beer • 350 mL of alcohol-free beer Consumed within 5 minutes
Outcomes	• Systolic blood pressure • Diastolic blood pressure • Heart rate • Pulse pressure Measured at baseline and at 30, 60, and 90 minutes after ingestion
Notes	• All participants habitually consumed alcohol-containing beverages, but none exceeded the recommended amount of beverage • All experiments were conducted after a light meal • No participants had chronic disease that could affect cardiovascular health, metabolism, or daily physical activity; none had a history of smoking; and none were taking any medications • All participants were asked to abstain from alcohol- and caffeine-containing beverages and to avoid strenuous physical activity for 12 hours before an experimental session • In addition, participants were advised to eat the same meals (breakfast, lunch, and dinner) on the day before each experimental session • We calculated MAP from reported SBP and DBP. SD for the MAP had to be imputed

Nishiwaki 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"All volunteers participated in four trials assigned in random sequence to four separate days" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All of the test drinks were poured into paper cups to maintain participant blinding (i.e. single-blind study)" Comment - blinding of participants was probably done
Blinding of outcome assessment (detection bias) All outcomes	High risk	"the same investigators performed all measurements" Comment - study was not blinded for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SEM
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP and SEM
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM
Other bias (conflict of interest, industry sponsorship)	Low risk	"The authors declare that there is no conflict of interests regarding the publication of this article" "This study was supported in part by a Grant-in-Aid from the Japanese Ministry of Education, Culture, Sports, Science and Technology to MN (JSPS KAKENHI Grant number JP 26750345)"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Potter 1986

Study characteristics	
Methods	Randomised controlled trial, double-blind, cross-over design
Participants	16 normotensive male medical students (8 with a family history of hypertension) with mean age of 22 years and mean body weight of 77 kg were included in the study
Interventions	• 0.75 g/kg body weight of alcohol in the form of beer, or • 600 mL of alcohol-free lager (Canada Dry Rawlings, Northants, UK) Consumed within 15 minutes
Outcomes	• Systolic blood pressure • Diastolic blood pressure • Pulse rate • Plasma catecholamines • Plasma cortisol and plasma renin activity • Plasma norepinephrine and epinephrine
Notes	• Washout period was 1 week between interventions • All participants abstained from alcohol, caffeine, and tobacco for 24 hours (although diet was otherwise unrestricted), and all fasted for 12 hours before each part of the study • Participants were considered to have a family history of hypertension if 1 or both parents had ever received treatment for hypertension or had a resting blood pressure of 160/95 mmHg or more • All participants were healthy and were taking no medication • We calculated MAP from reported SBP and DBP. SD for the MAP had to be imputed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Each subject then drank 600 ml of Barbican, an alcohol-free lager (Canada Dry Rawlings, Northants, UK) kept at room temperature, with or without the addition of 50% alcohol in a double-blind, random-order crossover design" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"At the end of each part of the study, subjects were asked to indicate whether they thought they had received the placebo (alcohol-free beer) or placebo with added alcohol" "Subjects were blinded to the order of treatment, and only eight of the 16 subjects recognized both stages correctly, indicating that the blinding procedure was reasonably successful" Comment - blinding of participants was probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment - method of blinding of outcome assessors was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment - all participants were included in the final analysis

Potter 1986 *(Continued)*

Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM in a figure
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	.Comment - study authors reported DBP and SEM in a figure
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP and SEM
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM in a figure
Other bias (conflict of interest, industry sponsorship)	Low risk	"Dr. Potter was supported by a research grant from the British Heart Foundation"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Rosito 1999

Study characteristics	
Methods	Randomised controlled trial, double-blind, parallel-group assignment
Participants	40 male medical students with mean age of 22.2 years were included in the trial
Interventions	• Water, or • 15, 30, or 60 g of ethanol in solutions containing citric acid (2.6 g) and glucose (35.6 g), with water to complete 500 mL, and lunch was provided immediately
Outcomes	• Systolic blood pressure • Diatolic blood pressure • Heart rate Measured every hour for 24 hours
Notes	• Participants were instructed to abstain from alcohol during the 3 days preceding the study • They slept in the hospital the night before the study period and consumed a balanced diet • They ate lunch immediately after the intervention • We calculated MAP from reported SBP and DBP. SD for the MAP had to be imputed

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Rosito 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Between 11:00 am and noon, according to a random allocation and without knowledge of exact ethanol content, the study subjects ingested water, 15, 30, or 60 g of ethanol" "The randomization (with random number allocator) was done in blocks of four" (information was given by study authors upon contacting) Comment - adequate randomisation was done
Allocation concealment (selection bias)	Low risk	"The randomization (with random number allocator) was done in blocks of four" (information was given by study authors upon contacting) Comment - adequate allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment - investigator who gave the drink was blinded to the content of alcohol, so adequate blinding of participants and personnel was done (information was given by study authors upon contacting)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The data were analyzed in a blinded fashion using analysis of variance (ANOVA) for repeated measurements and multiple factors to assess the effects of quantity of ethanol ingested, time after ingestion, and their interaction" Comment - blinding of outcome assessment was probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM in a figure
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SEM in a figure
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP and SEM
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM in a figure
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not report any conflict of interest nor sponsorship
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Rossinen 1997

Study characteristics	
Methods	Randomised controlled trial, open-label, cross-over design
Participants	20 individuals (17 men and 3 women, aged 39 to 68 years) with angiographically verified coronary heart disease and electrocardiographic evidence of myocardial ischaemia were included in the study Inclusion criteria: • Patients with luminal diameter narrowing ≥ 50% in at least 1 of the major epicardial coronary arteries and ischaemia verified by exercise test within 6 months were eligible for the study Exclusion criteria: • Patients with acute myocardial infarction within 1 month, New York Heart Association Class IV symptoms, luminal diameter narrowing ≥ 50% in the left main coronary artery or luminal diameter narrowing ≥ 80% in all 3 major epicardial vessels, ejection fraction ≤ 25% on left ventricular cineangiography • Previous sustained ventricular tachycardia or fibrillation, and • Presence of other than sinus rhythm, or • History of alcohol abuse
Interventions	• 1.25 g of ethyl alcohol per body weight in kilograms diluted to 15% juice, yielding volumes of 700 ± 126 mL, or • An equivalent volume of juice Participants were instructed to drink at an even pace over the 1 and 1/2 hours
Outcomes	• Heart rate variability • Systolic blood pressure
Notes	• Washout period: 7 ± 3 days (range 4 to 14) • Regular daily medication was continued throughout the study • 19 patients were taking β-blockers and long-acting nitrates, 17 aspirin, 7 calcium antagonists, and 4 angiotensin-converting enzyme inhibitors • 9 participants had arterial hypertension • 12 had had at least 1 myocardial infarction • None had diabetes mellitus • 7 participants had New York Heart Association Class II, and 13 participants Class III, symptoms • 8 participants had 1-vessel, 8 had 2-vessel, and 4 had 3-vessel disease on coronary angiography

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized to either alcohol or juice in a crossover manner" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias)	High risk	Comment - study was not blinded for outcome assessors

Rossinen 1997 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment - all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP with SD
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	High risk	Comment - study authors did not report DBP
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SD
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not report any conflict of interest nor sponsorship
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Stott 1987

Study characteristics	
Methods	Randomised controlled trial, open-label, cross-over design
Participants	10 healthy individuals (7 male, 3 female) aged 18 to 31 years with body weight of 56 to 101 kg
Interventions	• 1.3 g of alcohol/kg body weight, in the form of vodka made up to 1 litre with orange juice • 1 litre of orange juice made isocaloric with glucose
Outcomes	• Plasma noradrenaline and adrenaline • Systolic blood pressure • Diastolic blood pressure • Heart rate Measured at baseline (13.00), and at 14.00, 15.00, 16.00, 17.00, 19.00, and 22.00 hours that day; 09.00 and 14.00 hours the next day; and 14.00 hours for a further 5 days
Notes	• Participants' daily average alcohol consumption was 26 g • Participants had a light lunch at mid-day • For 1 week before and during each study phase, participants drank no other alcohol

Stott 1987 *(Continued)*

- For 3 days before and throughout each study phase, diet was controlled within individuals by careful recording in study phase 1 and replication of dietary intake in phase 2 by each participant
- We calculated MAP from reported SBP and DBP. SD for the MAP had to be imputed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"In a randomized, balanced, crossover study the effects of 1.3 g of alcohol/kg body weight, in the form of vodka made up to 1 litre with orange juice, were compared with 1 litre of orange juice made isocaloric with glucose (1 g alcohol = 7 kcal)" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	“Results were assessed independently by two observers” Comment - study was not blinded for outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment - all 10 participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM in a figure
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SEM in a figure
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP and SEM
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM in a figure
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not report any conflict of interest nor sponsorship
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Stott 1991

Study characteristics	
Methods	Randomised controlled trial, open-label, cross-over design
Participants	8 normotensive elderly participants (6 male, 2 female) with mean age of 81 years (range 70 to 96 years) and mean body weight of 68.4 kg were included in the study
Interventions	• 0.5 g of alcohol/kg of body weight, in the form of vodka made up to 200 mL with unsweetened orange juice • 200 mL of orange juice alone Each consumed over 15 minutes
Outcomes	• Systolic blood pressure • Diastolic blood pressure • Heart rate • Plasma sodium and potassium • Blood alcohol • Blood sugar Baseline recording was taken at 1:00, and further recordings were taken at 1:30, 2:00, 3:00, and 4:00 PM
Notes	• .All had sitting systolic and diastolic blood pressures of 110 to 180 mmHg and < 100 mmHg, respectively, and normal orthostatic responses with a reduction in systolic blood pressure < 10 mmHg on standing • Participants were moderate to occasional drinkers with a usual weekly alcohol intake of 2.0 to 1.1 (maximum 7) units (1 unit = 10 g) • Participants were non-smokers • 2 participants had a history of cerebrovascular disease, 1 had chronic obstructive airways disease, and 1 had peripheral vascular disease • All participants had a normal resting electrocardiogram, and none were taking cardioactive drugs • Participants drank no other alcohol for 24 hours before each study day • No other food or drink was allowed between 12 noon and 4:00 PM on study days • Participants had a standard light lunch at midday (12 noon) • We calculated MAP from reported SBP and DBP. SD for the MAP had to be imputed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"In a randomized, balanced, crossover study design, the effects of 0.5 g of alcohol/kg body weight, in the form of vodka made up to 200 mls with unsweetened orange juice, were compared with the effects of 200 mls of orange juice alone, each consumed over 15 minutes" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel

Stott 1991 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment - all 8 participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SEM in a figure
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SEM in a figure
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP and SEM
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM in a figure
Other bias (conflict of interest, industry sponsorship)	Unclear risk	Comment - study authors did not report any conflict of interest nor sponsorship
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Van De Borne 1997

Study characteristics	
Methods	Randomised controlled trial, double-blinded, cross-over design
Participants	16 normal male individuals with mean age of 26 ± 4 (SD) years
Interventions	• Alcohol (1.0 g/kg body weight, diluted in 400 mL of water) • 400 mL of water Consumed over 30 minutes
Outcomes	• Blood pressure • Heart rate • Heart rate variability • Muscle sympathetic nerve activity • Forearm vascular resistance • Minute ventilation

Van De Borne 1997 *(Continued)*

	Measured at baseline and at 45, 60, and 80 minutes after ingestion
Notes	• None was taking any medications • Participants were fed and hospitalised in the Clinical Research Center for approximately 4 hours after alcohol intake, after which they were driven home • All studies were performed with participants in the fasting state to avoid changes in muscle SNA and in alcohol absorption induced by food intake

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A flavoring (Crystal Light) was added to these solutions to prevent the subjects from distinguishing the alcohol from the vehicle session" Comment - adequate blinding of participants and personnel was probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Measurements were made by a single observer (P. van de B.) in a blinded fashion" "Statisical analysis was performed by an independent statistician" Comment - adequate blinding of outcome assessment was done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	High risk	Comment - study authors did not report SBP
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	High risk	Comment - study authors did not report DBP
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	Low risk	Comment - study authors reported MAP and SEM in a figure
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SEM in a figure
Other bias (conflict of interest, industry sponsorship)	Low risk	"These studies were also supported by a Grant-in-Aid from the American Heart Association, National Institutes of Health (NIH) grants HL-14388 and HL-24962, and an NIH Sleep Academic Award"

Van De Borne 1997 *(Continued)*

Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Williams 2004

Study characteristics	
Methods	Randomised controlled trial, open-label, cross-over design
Participants	14 men with mean age of 59 ± 7 (SD) years and body weight of 86 ± 13 (SD) kg were included in the study Inclusion criteria: • Men with angiographic evidence of coronary artery disease (CAD) Exclusion criteria: • Men who had experienced an acute coronary event within the preceding 60 days; had significant renal or hepatic disease, uncontrolled hypertension, diabetes mellitus, a recent history of smoking cigarettes, a history of alcohol dependence or abuse; or were receiving oral anticoagulant therapy
Interventions	• Red wine (Stoneleigh Marlborough Pinot Noir, New Zealand, 1998) or white wine (Jackson Estate Marlborough Sauvignon Blanc, New Zealand, 1998) at a dose of 0.52 g alcohol/kg body weight • Isoenergetic, non-alcoholic beverage (raspberry cordial: Schweppes, Auckland, New Zealand)
Outcomes	• Plasma levels of IL-6 • Systolic blood pressure • Diastolic blood pressure • Heart rate • Plasma concentrations of soluble cell adhesion molecules BP and HR were measured at baseline and at 1 hour and 6 hours after consumption
Notes	• Self-reported drinking habits of participants were recorded • Participants were instructed to refrain from drinking alcohol for 1 week before each study visit • On study days, men were instructed to consume a light breakfast consisting of 2 slices of toast with jam at home before reporting to the study centre at 9 AM. Tea, coffee, and fruit juices were not permitted • Test beverages were consumed with a light meal that was low in antioxidants. This meal was designed to minimise the influence of nutrient and antioxidant intake on study variables while complying with the dictum that alcoholic beverages should be consumed with food. The meal consisted of a small bread roll (58 g) filled with 5 g margarine, 2 leaves of lettuce, half a tomato sliced, a slice of low-fat cheese (25 g), low-fat yogurt (200 g), and a banana (total energy, 2,222 kJ (513 kcal); carbohydrate, 62% energy; protein, 18% energy; fat, 20% energy) • During the following 6-hour test period, participants did not consume any food and were permitted only bottled water to drink • Washout period between wine interventions was at least 1 week • 3 months after the wine study, participants ingested an isoenergetic, non-alcoholic beverage with the light meal in an identical protocol • All men were receiving aspirin therapy, and most were also receiving treatment with statins and β-blocking drugs. Approximately half of the men were taking angiotensin-converting enzyme (ACE) inhibitor drugs • Nearly all of the men were light to moderate consumers of alcohol

Williams 2004 *(Continued)*

We calculated MAP from reported SBP and DBP. SD for the MAP had to be imputed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomized to receive red wine (Stoneleigh Marlborough Pinot Noir, New Zealand, 1998) or white wine (Jackson Estate Marlborough Sauvignon Blanc, New Zealand, 1998) followed by the alternate wine with an interval of at least a week between each intervention" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One subject was excluded from the present study due to insufficient stored plasma for measurement of cytokines at all time points" Comment - reasons for exclusion of participants were reported and balanced across groups, so missing data should not affect the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP with SD
Selective reporting (reporting bias) For diastolic blood pressure (DBP)	Low risk	Comment - study authors reported DBP and SD
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SD
Other bias (conflict of interest, industry sponsorship)	Low risk	"Supported by the Cardiology Department Research Fund"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

Zeichner 1985

Study characteristics	
Methods	Randomised controlled trial, open-label, parallel-group assignment
Participants	48 healthy psychology undergraduate students (24 male and 24 female) with mean age of 20.9 ± 2.18 (SD) years (range 19 to 23)
Interventions	• 1 g/kg body weight of 95% USP alcohol in a mixture of 1 part alcohol to 5 parts orange juice • Orange juice All participants were told that they must consume the first drink within 10 minutes and the second drink within the subsequent 10 minutes
Outcomes	• Systolic blood pressure • Diastolic blood pressure • Heart rate Baseline and 40 minutes after alcohol consumption
Notes	• Participants abstained from alcoholic beverages for a minimum of 24 hours, and from coffea, tea, cigarettes, and food for at least 4 hours before the experimental session • We calculated MAP from reported SBP and DBP. SD for the MAP had to be imputed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Healthy college age males and females classified as type A and Type B were randomly assigned to an alcohol group or a no alcohol group" Comment - method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Comment - method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment - study was not blinded for participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment - study was not blinded for outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment - it is not explicitly mentioned whether all participants were included in the final analysis
Selective reporting (reporting bias) For systolic blood pressure (SBP)	Low risk	Comment - study authors reported SBP and SD
Selective reporting (reporting bias)	Low risk	Comment - study authors reported DBP and SD

Zeichner 1985 *(Continued)*

For diastolic blood pressure (DBP)		
Selective reporting (reporting bias) For mean arterial blood pressure (MAP)	High risk	Comment - study authors did not report MAP
Selective reporting (reporting bias) For heart rate (HR)	Low risk	Comment - study authors reported HR and SD
Other bias (conflict of interest, industry sponsorship)	Low risk	"This research was supported in part by a grant from the University of Georgia Research Foundation, Inc"
Other bias (was the study registered in clinical trials.gov/ was the protocol available?)	High risk	Comment - protocol was not registered and study identifier was not reported

ACE: angiotensin-converting enzyme.
ADH: alcohol dehydrogenase.
AIx: augmentation index.
BAC: blood alcohol concentration.
BMI: body mass index.
BP: blood pressure.
bpm: beats per minute.
CAD: coronary artery disease.
DBA: diameter of brachial artery.
DBP: diastolic blood pressure.
DRW: de-alcoholised red wine.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
EtOH: ethanol.
HbA1c: glycosylated haemoglobin.
HETE: hydroxyeicosatetraenoic acid.
HR: heart rate.
HRV: heart rate variability.
IL-6: interleukin-6.
MAP: mean arterial pressure.
MDMA: methylenedioxymethamphetamine.
NE: norepinephrine.
NSAID: non-steroidal anti-inflammatory drug.
SBP: systolic blood pressure.
SD: standard deviation.
SEM: standard error of the mean.
SNA: sympathetic nervous activity.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abrams 1979	This study used the wrong study design. Heart rate measurements in this study were divided into 14 phases, and all 14 phases were affected by social anxiety (stress)
Abu-AmshaCaccetta 2001	This study used the wrong study design. Because the intervention was consumed continuously for 2 weeks and measurements were made only after 2 weeks, this study did not meet our inclusion criteria

Study	Reason for exclusion
	"Volunteers were randomly allocated to drink either: (i) 375 ml of red wine (Shiraz-Grenache Blend, 13.3% alc/vol, 1200 mg/l polyphenols); or (ii) 375 ml of white wine (Deakin Estate, Chardonnay, 13.7% alc/vol, 345 mg/l polyphenols) 'polyphenol control'; or (iii) 500 ml of the same red wine but dealcoholized (< 2% alc/vol, 905 mg/l polyphenols) 'alcohol control,' each evening for 2 weeks, with a 1 week washout at the start of the study and between each beverage"
Adamsson 2011	This study used the wrong intervention. Nordic diet containing 27%, 52%, 19%, and 2% of energy from fat, carbohydrate, protein, and alcohol, respectively, was used as an intervention in this study. Because only 2% alcohol was contributed in this diet, alcohol was not the major intervention in this study
Aguilar 2004	This study used the wrong study design because alcohol consumption was self-reported "Patients were classified as non-drinkers, light to moderate drinkers or heavy drinkers based on alcohol consumption reported at baseline"
Aigner 2016	This was a case control study, so this study used the wrong study design "We performed a case-control study based on a sample of 3308 stroke patients aged 18 to 55 years"
Ajani 2000	This study used the wrong study design because alcohol consumption was self-reported "We used four categories of alcohol intake at baseline - rarely/never, monthly, weekly, and daily"
Almeida 2014	This study used the wrong study design because alcohol consumption was self-reported "We then asked men whether they had drunk alcohol during the last year (yes/no). Those who answered yes were required to indicate how many standard drinks of alcohol they consumed each usual day (from Monday to Sunday)"
Andres-Lacueva 2013	This study used the wrong intervention because it examined the effect of red wine polyphenols rather than the effect of alcohol
Anil 2016	Alcohol was not given as an intervention in this study, and this study focused on the dietary pattern; hence this study used the wrong intervention and the wrong study design
Apostolidou 2015	This was not a randomised controlled trial and red wine tannat rather than alcohol was given as an intervention; hence this study used the wrong study design and the wrong intervention
Appel 2003	This study used the wrong intervention because alcohol was not used as an intervention
Argani 2016	Red grape seed extract (RGSE) was used as the intervention in this study; hence this study used the wrong intervention
Ariansen 2009	Losartan- or atenolol-based antihypertensive therapy was used as the intervention rather than alcohol in this study; hence this study used the wrong intervention
Ariansen 2012	Losartan- or atenolol-based antihypertensive therapy was used as the intervention rather than alcohol in this study; hence this study used the wrong intervention
Assaad 2006	This study used the wrong study design because it was not a placebo-controlled study "Participants were explicitly told what they drank, and no placebo control group was used"
AuYeung 2013	This study used the wrong study design because it was a cohort study and alcohol consumption was self-reported

Study	Reason for exclusion
Avellone 2006a	This study examined the effects of 2 different red wines. It was not placebo-controlled; hence this study used the wrong study design
Avellone 2006b	This study compared the effects of 2 different red wines rather than using a placebo control group; hence this study used the wrong study design
Bae 2015	Alcohol was not used as an intervention in this study. Bisphenol A (BPA) from canned beverages was examined in this study; hence this study used the wrong intervention
Bailey 1989	This study used the wrong intervention and the wrong outcome. Alcohol was not the only intervention given in this study. Blood pressure and heart rate were recorded but only when felodipine was given
Bailey 2003	Alcohol was not used as an intervention in this study; hence this study used the wrong intervention
Banini 2006	The intervention provided in this study consisted of muscadine grape products rather than ethanol; hence this study used the wrong intervention
Barden 2007	This study used the wrong study design because it examined the reduction effect of alcohol "[Participants] were randomized to either continue their usual alcohol intake or reduce their alcohol intake..."
Barden 2017	Blood pressure was measured at baseline and after each intervention period (4 weeks), which was not considered an acute effect of alcohol; hence this study used the wrong study design
Baros 2008	This study used the wrong study design. Alcohol was not given as an intervention in this study. Alcohol consumption was self-reported by participants during a specific period of time
Barskova 2005	Metformin rather than alcohol was used as an intervention in this study; hence this study used the wrong intervention
Beevers 1987	Alcohol consumption was self-reported in this study; hence this study used the wrong study design
Beilin 1992	This study was a review; hence this study used the wrong study design
Beilin 1994	Alcohol was not used as an intervention in this study; hence this study used the wrong intervention
Beilin 1996	This study was a review; hence this study used the wrong study design
Bengtsson 1973	This was an epidemiological study; hence this study used the wrong study design
Berg 2005	This was an epidemiological study; hence this study used the wrong study design
Berglund 1989	Alcohol was not used as an intervention in this study. Decreasing the consumption of alcohol and changing diet (increasing ratio of polyunsaturated to saturated fat, and increasing potassium intake) were used as interventions in this study; hence this study used the wrong interventions
Bermudez 2015	This study used the wrong study design. Alcohol consumption was measured by asking participants to estimate the number of alcoholic drinks they consumed within a month; hence this study was based on self-report
Beulens 2005	Intervention duration of this study was 3 weeks, and neither blood pressure nor heart rate was recorded; hence this study used the wrong study design and the wrong outcomes

Study	Reason for exclusion
Beyeler 1987	This study used the wrong intervention. Alcohol was not given as the only intervention. It was given with disulfiram treatment
Bjorntorp 1999	This study used the wrong intervention because alcohol was not provided as an intervention
Blankenhorn 1990	Alcohol was not the main intervention in this study, and data collected were self-reported; hence this study used the wrong intervention and the wrong study design
Bleich 2001	The intervention duration was 6 weeks for each intervention, which was not considered an acute effect; hence this study used the wrong study design
Bold 2017	Alcohol consumption and data collected were self-reported; hence this study used the wrong study design
Bond 1984	This study used the wrong study design. Even though alcohol was the major intervention, measurements of heart rate and blood pressure were made only after exercise, and when the heart rate of 150 beats/min was reached "The subject then ingested the experimental liquid in five equal parts over a 10 minute period. After a 30 minute absorption period, fingertip blood samples were collected for determining blood alcohol levels. After completion of the absorption period, work bouts on the ergometer were initiated. Measures of heart rate, blood pressure, oxygen uptake and ventilation were recorded each minute after a heart rate of 150 beats/min was reached"
Botden 2011	Red wine polyphenols rather than alcohol were given as the intervention; hence this study used the wrong intervention
Botden 2012	Red wine polyphenols rather than alcohol were given as the intervention; hence this study used the wrong intervention
Brader 2011	Nordic diet rather than alcohol was given as an intervention; hence this study used the wrong intervention
Bradford 1990	Lovastatin was given as an intervention in this study; hence this study used the wrong intervention
Braggio 1992	This was not a randomised controlled trial and it was questionnaire-based; hence this study used the wrong study design
Brainin 2016	Lifestyle modification rather than alcohol was used as an intervention in this study; hence this study used the wrong intervention
Brasser 2004	Alcohol was not given as the only intervention in this study. The main purpose of this study was to examine the effect of alcohol on acamprosate; hence this study used the wrong intervention
Brewer 2010	Alcohol was not used as an intervention in this study; hence this study used the wrong intervention
Brien 1979	Alcohol was given with calcium carbimide in this study; hence this study used the wrong intervention
Brown 1981	Alcohol was not given as the only intervention in this study; hence this study used the wrong intervention
Brown 2010	This randomised controlled trial was double-blinded and placebo-controlled. Even though heart rate was recorded, heart rate could not be analysed due to technical failure and was not reported in this study

Study	Reason for exclusion
Brugger-Andersen 2009	Alcohol consumption was self-reported, and this study was not a randomised controlled trial; hence this study used the wrong study design
Brunelle 2007	This study was neither a randomised controlled trial nor a placebo-controlled trial; hence this study used the wrong study design
Bryson 2008	This was an analysis of cohort study data; hence this study used the wrong study design
Bulpitt 1999	This study examined the effects of alcohol reduction; hence this study used the wrong study design
Burke 2001	Moderation of lifestyle was used as an intervention rather than alcohol; hence this study used the wrong intervention
Burke 2005	Alcohol was not the main intervention in this study; hence this study used the wrong intervention
Burke 2006	Moderation of lifestyle was used as an intervention rather than alcohol; hence this study used the wrong intervention
Campbell 1999	Lifestyle modification was the main intervention in this study; hence this study used the wrong intervention
Carter 2011	This study used the wrong study design. Even though it had met all inclusion criteria, measurements were influenced by lower body negative pressure (LBNP), which resulted in displacement of blood away from the upper body to the abdomen and the lower extremities; hence results of this study could not be considered "Subjects were then placed in the supine position, with the bottom portion of their body in a LBNP chamber" "Subjects underwent a 5-min resting baseline, followed by a progressive LBNP protocol of 3 min each at -5, -10, -15, -20, -30, and -40 mmHg (pretreatment)"
Chagas 2016	This was a cross-sectional study; hence this study used the wrong study design
Chang 2011	This study was interview-based; hence this study used the wrong study design
Chaplin 2008	Alcohol was not given as the intervention in this study; hence this study used the wrong intervention and the wrong study design
Chaudhuri 1994	This study was not a randomised controlled trial; hence this study used the wrong study design
Chiadak 2017	Data collected in this study were questionnaire-based; hence this study used the wrong study design
Childs 2011	Even though this study was a randomised controlled trial and was placebo-controlled, neither blood pressure nor heart rate was reported after the intervention. Only baseline heart rate and blood pressure were measured
Chiva-Blanch 2012a	The intervention duration of this study was 4 weeks, which was not considered an acute effect; hence this study used the wrong study design
Chiva-Blanch 2012b	Blood pressure was measured at the end of the intervention duration of 4 weeks, which was not considered an acute effect; hence this study used the wrong study design
Chiva-Blanch 2013a	Even though this study was a randomised controlled trial and a cross-over study, it was not placebo-controlled; hence this study used the wrong study design

Study	Reason for exclusion
Chiva-Blanch 2013b	Blood pressure was measured at the end of the intervention duration of 4 weeks, which was not considered an acute effect; hence this study used the wrong study design. In addition, neither blood pressure nor heart rate was recorded; hence this study used the wrong outcomes
Chiva-Blanch 2015	The intervention duration of this study was 4 weeks, which was not considered an acute effect; hence this study used the wrong study design
Colby 2004	The main purpose of this study was irrelevant to the interests of our review. This study compared tobacco to alcohol; hence this study used the wrong main intervention
Conen 2008	This was a prospective study; hence this study used the wrong study design
Cordain 2000	This study used the wrong study design because the intervention duration was 10 weeks, which was not considered an acute effect
Covault 2014	This study used the wrong intervention because alcohol was not given as the only intervention "...pretreatment with 4mg dutasteride or placebo was paired with a moderate dose of alcohol (0.8 g/kg) or placebo beverage"
Cox 1990	This study used the wrong study design because it examined the effects of alcohol reduction
Cox 1993	This study used the wrong study design because it examined the effects of alcohol reduction
Croissant 2011	This study was not placebo-controlled; hence this study used the wrong study design
Cushing 2009	This study used the wrong intervention as participants received placebo of PM 101 as the intervention "...receiving placebo (5% dextrose in water, n=112) or PM101 (bolus push, n=112)"
Cushman 1994	This study used the wrong study design because it examined the effects of alcohol reduction
Cushman 1998	The intervention of this study was reduction of alcohol; hence this study used the wrong intervention
Cutler 1991	Reduction of alcohol was performed in this study and alcohol was not the main intervention; hence this study used the wrong study design and the wrong intervention
deLorenzo 1985	This study used the wrong intervention because ketanserin was used as the main intervention
deLorenzo 1988	This study used the wrong intervention because serotonin antagonist was used as the main intervention
Demmler 2013	This was a cross-sectional study; hence this study used the wrong study design
deRijke 1996	This study used the wrong study design because it was not placebo-controlled. Red wine was compared to white wine instead of to placebo
DiGarbo 2004	This study used the wrong study design because it was not placebo-controlled
Dimmitt 1998	This study used the wrong study design because it examined the effects of alcohol reduction
Draijer 2015	This study used the wrong intervention because grape extracts were used as the intervention instead of alcohol

Study	Reason for exclusion
Droste 2013a	This study used the wrong study design because the intervention duration was 20 weeks, which was not considered an acute effect
Droste 2013b	This study used the wrong study design because the intervention duration was 20 weeks, which was not considered an acute effect
Durocher 2011	Study authors were contacted, but required data were not reported in the study
Eisenhofer 1987	This study used the wrong outcomes because reported blood pressure was accompanied by information on the effects of cold pressor
Estevez 1995	This study used the wrong comparator and was not placebo-controlled. Alcohol was compared to ritanserin instead of to placebo; hence this study used the wrong study design
Estruch 2011	This study used the wrong study design because the intervention duration was 28 days, which was not considered an acute effect
Farre 1993	This study used the wrong intervention because alcohol was given with cocaine as the intervention
Farre 2014	This study used the wrong comparator and was not placebo-controlled. Alcohol was compared to soy extract in this study; hence this study used the wrong study design
Farre 2016	This study used the wrong intervention because alcohol was given with mephedrone
Farre 2017	This study used the wrong intervention because alcohol was given with mephedrone
Fazio 2001	This study used the wrong study design because it was questionnaire-based "The study was performed in 10 young healthy male volunteers whose weekly ethanol consumption was estimated by questionnaire to be less than 100g"
Flanagan 2002	This study used the wrong study design because the intervention duration was 1 week, which was not considered an acute effect
Flechtner-Mors 2004	This study used the wrong study design because the intervention duration was 3 months, which was not considered an acute effect
Foltin 1988	This study used the wrong intervention because alcohol was ingested with cocaine
Foppa 1999	Full text of this study was not available, and contact information for study authors could not be found
Frisk-Holmberg 1990	This study used the wrong intervention because jian bu wan was given as the intervention instead of alcohol
Garcia-Andrade 1997	Even though this study met all the inclusion criteria, placebo data were not reported. Study author was contacted via email for additional information but this author refused to disclose unpublished data. Hence, we excluded this study
Gepner 2013	This study used the wrong study design because the intervention duration was 6 months, which was not considered an acute effect
Gepner 2015	This study used the wrong study design because the intervention duration was 2 years, which was not considered an acute effect

Study	Reason for exclusion
Gepner 2016	This study used the wrong study design because the intervention duration was 6 months, which was not considered an acute effect
Giovannelli 2011	This study used the wrong intervention because it provided de-alcoholised red wine with different concentrations of polyphenols as the intervention instead of alcohol
Golan 2016	This study used the wrong study design because the intervention duration was 2 years, which was not considered an acute effect
Golan 2017	This study used the wrong study design because the intervention duration was 2 years, which was not considered an acute effect
Golan 2018	This study used the wrong study design because the intervention duration was 2 years, which was not considered an acute effect
Gopane 2010	This study used the wrong study design because it was a cross-sectional study
Gourlay 2013	Full text was not available for this study, and contact information for study authors was not found
Greyling 2016	This study used grape juice and wine polyphenols as the intervention instead of alcohol; hence this study used the wrong intervention. In addition, this study used the wrong study design because the intervention duration was 8 weeks, which was not considered an acute effect
Hansen 2005	This study used the wrong study design because the intervention duration was 4 weeks, which was not considered an acute effect
Hartmann 2017	Full text was not available for this study, and contact information for study authors was not found
Hijmering 2007	This study was not placebo-controlled; hence this study used the wrong study design "In 45 minutes, three units of red wine or an alcoholic beverage with a low polyphenolic count [was] consumed"
Howes 1985	The effect of alcohol on blood pressure was measured on the fifth day after 4 days of intervention; hence this study used the wrong study design
Howes 1986a	This study used the wrong study design as the intervention duration was 4 days
Howes 1986b	Even though this study met all the inclusion criteria, only data on the effect of alcohol with no-radrenaline on blood pressure were reported, and no author contact information was provided. Hence, we excluded this study
Jacobs 2012	This study used the wrong comparator because red wine was compared to grape juice extracts
Jain 2016	This study used the wrong study design because the intervention duration was 2 years, which was not considered an acute effect
Jones 1979	This study used the wrong intervention because it examined the effect of alcohol combined with hyperbaric air
Kaul 2010	This study used the wrong study design because the intervention duration was 2 weeks, which was not considered an acute effect
Kawano 1998	The effect of alcohol on blood pressure was measured after 4 days of intervention; hence this study used the wrong study design

Study	Reason for exclusion
Kawano 2002	The alcohol reduction effect was examined in this study; hence this study used the wrong study design
Kawano 2004	This study included 3 phases: control phase, alcohol phase, and recovery phase. The placebo-controlled group was not present throughout the study; hence this study used the wrong study design
Kechagias 2015	This study used the wrong study design because the intervention duration was 3 months, which was not considered an acute effect
Kelbaek 1987	This study met all inclusion criteria. However, control group data were not reported, and no author contact information was provided. Thus, we excluded this study
Kelbaek 1988	This was not a randomised controlled trial; hence this study used the wrong study design
Kino 1981	This was not a randomised controlled trial; hence this study used the wrong study design
Koskinen 1991	Alcohol consumption was self-reported in this study; hence this study used the wrong study design
Lachtermann 1999	This study met all the inclusion criteria. However, heart rate and blood pressure were not reported, and no author contact information was provided. Thus, we excluded this study
Latella 2009	This was a cross-sectional study; hence this study used the wrong study design
Lavy 1994	This study used the wrong study design because it was not placebo-controlled. Red wine was compared to white wine instead of to placebo
Lee 2002	This was a review; hence this study used the wrong study design
Lee 2016	Data reported in this study were questionnaire-based and were self-reported; hence this study used the wrong study design
Li 2006	This was a cross-sectional study; hence this study used the wrong study design
Li 2016	This was an observational analysis; hence this study used the wrong study design
Liang 2012	This was an observational study; hence this study used the wrong study design
Malinski 2004	Data reported in this study were self-reported. This was a cross-sectional study; hence this study used the wrong study design
Mammen 2018	This study used the wrong study design. Alcohol was compared to placebo or to low-dose polyphenol. The purpose of this study was irrelevant to the interest of this review
Marczinski 2018	Alcohol was not given alone as the intervention. Energy drink was also given to participants. Thus, this study provided the wrong intervention
McCance-Katz 1996	This study used the wrong intervention because alcohol was given with cocaine
McCance-Katz 2005	This study used the wrong intervention because alcohol was given with cocaine
McCance-Katz 2013	This study used the wrong intervention because alcohol was given with ritonavir or efavirenz
McCaul 1991	This study used the wrong intervention because alcohol was given with secobarbital
McDonagh 2018	This study used the wrong intervention. Alcohol was not given as the only intervention in this study

Study	Reason for exclusion
McDougle 1995	This study used the wrong intervention because yohimbine was provided as the main intervention instead of ethanol
Mezzano 2001	This study used the wrong intervention and the wrong study design. Participants received either MD (Mediterranean-type diet) or HFD (high-fat diet) for 90 days, and both diets were supplemented with red wine on day 30 and on day 90. Thus, this study did not include a placebo control group, and the intervention duration was too long to be considered an acute effect
Mezzano 2003	This study used the wrong intervention and the wrong study design. Participants received either MD (Mediterranean-type diet) or HFD (high-fat diet) for 90 days, and both diets were supplemented with red wine on day 30 and on day 90. Thus, this study did not include a placebo control group, and the intervention duration was too long to be considered an acute effect
Minami 2002	This study used the wrong study design because the effect of alcohol reduction was examined
Mizushima 1990	In this cross-sectional study, alcohol consumption was self-reported; hence this study used the wrong study design
Molnar 2009	This study used the wrong study design because it was not a randomised controlled trial
Moreira 1998	Alcohol consumption was self-reported in this study; hence this study used the wrong study design
Mori 2015	This study used the wrong study design because the intervention duration was 4 weeks
Mori 2016	This study used the wrong study design because the intervention duration was 4 weeks, which was not considered an acute effect
Movai 1989	This was not a randomised placebo-controlled study
Mukamal 2017	This study used the wrong study design because the intervention duration was 6 months. Even though participants returned monthly for measurement, this was still not considered an acute effect
Naissides 2006a	This study used the wrong study design because the intervention duration was 6 weeks, which was not considered an acute effect
Naissides 2006b	This study used the wrong study design because the intervention duration was 6 weeks, which was not considered an acute effect
Newlin 1989	This study was not a randomised controlled trial; hence this study used the wrong study design
Newlin 1990	This study used the wrong outcomes because only heart rate change before and after the intervention was measured
Niaura 1988	This was not a randomised controlled trial; hence this study used the wrong study design
Nicholas 2012	Full text was not available for this study, and contact information for study authors was not found
Nicholas 2013a	Full text was not available for this study, and contact information for study authors was not found
Nicholas 2013b	Full text was not available for this study, and contact information for study authors was not found
Noad 2016	Alcohol was not the intervention used in this study. Polyphenol was used as the intervention. Thus, this study used the wrong intervention

Study	Reason for exclusion
O'Malley 2014	This study used the wrong study design because there was no placebo-controlled group. Only low, medium, and high doses of alcohol were given to participants
Oda 2017	This study used the wrong study design because alcohol consumption was self-reported
Okamura 2001	This was a cross-sectional study; hence this study used the wrong study design
Papamichael 2006	The effect of alcohol accompanied by smoking rather than the effect of alcohol alone was examined; hence this study used the wrong intervention
Papamichael 2008	This study used the wrong intervention because alcohol was not given as the only intervention. It was accompanied by olive oil
Papaseit 2016	This study used the wrong intervention because alcohol was given with mephedrone rather than alone
Park 2004	This study used the wrong intervention. Concord grape juice was given as the intervention instead of alcohol
Parker 1990	This study used the wrong study design because the effect of alcohol reduction was examined
Paz 1996	This study used the wrong study design because it was not a randomised controlled trial
Perkins 1995	This study used the wrong intervention because the combined effect of alcohol and nicotine was examined instead of the effect of alcohol alone
Perneger 1999	Alcohol consumption was self-reported in this study; hence this study used the wrong study design
Petrone 2014	Alcohol consumption was self-reported in this study; hence this study used the wrong study design
Pisa 2010	This study was a cross-sectional epidemiological survey; hence this study used the wrong study design
Pitsavos 2004	This study was an epidemiological study; hence this study used the wrong study design
Potter 1984	This study used the wrong study design. The intervention duration was 4 days, and measurements were made after the intervention duration; thus this was not considered an acute effect
Puddey 1985a	This study used the wrong study design. The intervention duration was 6 weeks, and measurements were made after the intervention duration; thus this was not considered an acute effect
Puddey 1985b	Alcohol reduction was examined in this study; hence this study used the wrong study design
Puddey 1985c	Alcohol reduction was examined in this study; hence this study used the wrong study design
Puddey 1986	Alcohol reduction was examined in this study; hence this study used the wrong study design
Puddey 1987	This study used the wrong study design because changes in alcohol consumption were self-reported and the intervention duration was 6 weeks, which was not considered an acute effect
Puddey 1992	This study used the wrong study design because alcohol reduction was examined and the intervention duration was 18 weeks, which was not considered an acute effect
Rada 2018	This study used the wrong study design. The intervention duration was 4 weeks, and measurements were made after the intervention period, which was not considered an acute effect

Study	Reason for exclusion
Rajdl 2007	This study used the wrong study design because it was not placebo-controlled. This study examined only the effect of white wine but did not compare this to the placebo control
Rakic 1998	Alcohol reduction effect was examined in this study; hence this study used the wrong study design
Retterstol 2005	This study used the wrong study design. The intervention duration was 3 weeks, and measurements were made at the end of the study, which was not considered an acute effect
Roache 2011	This study used the wrong intervention because it examined the combined effect of cocaine and alcohol instead of the effect of alcohol only
Roth 2013	This study used the wrong study design. The intervention duration was 1 month, and measurements were made at the end of the study, which was not considered an acute effect
Roth 2017	This study used the wrong study design. The intervention duration was 3 weeks, and measurements were made at the end of the study, which was not considered an acute effect
Roth 2018	This study used the wrong study design. The intervention duration was 3 weeks, and measurements were made at the end of the study, which was not considered an acute effect
Sagawa 2011	This was not a randomised controlled trial; hence this study used the wrong study design
Saito 2003	This was a cross-sectional study; hence this study used the wrong study design
Sehested 1998	This study was not placebo-controlled; hence this study used the wrong study design. Participants were divided into 2 groups: Group A: alcohol mixed with 500 mL of juice; Group B: similar to Group A plus 750 mL of mineral water. Group B did receive alcohol even though it was mixed with mineral water; hence this was a placebo-controlled group
Senault 2000	This study used the wrong study design. The intervention duration was 14 days, and measurements were made at the end of the study, which was not considered an acute effect
Shai 2007	This study used the wrong study design. The intervention duration was 3 months, and measurements were made at the end of the study, which was not considered an acute effect
Shai 2015	This study used the wrong study design. The intervention duration was 2 years, and measurements were made at the end of the study, which was not considered an acute effect
Sierksma 2002	This study used the wrong study design. The intervention duration was 3 weeks, and measurements were made at the end of the study, which was not considered an acute effect
Sierksma 2004a	This study used the wrong study design. The intervention duration was 3 weeks, and measurements were made at the end of the study, which was not considered an acute effect
Sierksma 2004b	This study used the wrong study design. The intervention duration was 3 weeks, and measurements were made at the end of the study, which was not considered an acute effect
Spaak 2008	This study used the wrong study design because alcohol was given repeatedly to reach a certain blood pressure level. Thus, alcohol was not given at a particular dose; dose varied with the blood alcohol level of participants
Stiffler 1999	This study reported only the mean difference in heart rate between day and night; thus required data were not reported
Stream 2010	Full text was not available for this study, and contact information for study authors was not found

Study	Reason for exclusion
Stream 2014	Full text was not available for this study, and contact information for study authors was not found
Stuart 2013	This study used the wrong intervention because alcohol was not the main intervention used "...received 40h of standard batterer program or the standard batterer program and 90 min alcohol intervention"
Stubbs 1995	This study used the wrong intervention because the combined effect of alcohol and caffeine (coffee) was examined instead of the effect of alcohol alone
Taborsky 2012	This study was not placebo-controlled (compared red wine to white red); hence this study used the wrong study design
Taborsky 2014	This study was not placebo-controlled (compared red wine to white red); hence this study used the wrong study design
Takashima 1998	This was a cross-sectional study; hence this study used the wrong study design
Tinklenberg 1976	This study did not include a placebo for the alcohol
Tome-Carneiro 2012	This study used the wrong study design. The intervention duration was 1 year, and measurements were made at the end of the study, which was not considered an acute effect. In addition, this study used the wrong intervention because grape supplement was used as the main intervention instead of alcohol
Tome-Carneiro 2013	This study used the wrong study design. The intervention duration was 1 year, and measurements were made at the end of the study, which was not considered an acute effect. In addition, this study used the wrong intervention because resveratrol-containing grape extract was used as the main intervention instead of alcohol
TOMHS 1991	Alcohol was not used as the main intervention in this study; hence this study used the wrong intervention
Toth 2012	This study used the wrong study design. The intervention duration was 3 weeks, and measurements were made at the end of the study, which was not considered an acute effect
Toth 2014	This study used the wrong study design. The intervention duration was 3 weeks, and measurements were made at the end of the study, which was not considered an acute effect
Tresserra-Rimbau 2013	This study used the wrong study design. The intervention duration was 5 years, and measurements were made at the end of the study, which was not considered an acute effect
Tresserra-Rimbau 2015	This was a cross-sectional study; hence this study used the wrong study design
Tuomilehto 1984	Alcohol consumption was self-reported in this study; hence this study used the wrong study design
Turczynski 2001	Full text was not available for this study, and contact information for study authors was not found
Ueshima 1987a	Full text was not available for this study, and contact information for study authors was not found
Ueshima 1987b	Effects of alcohol reduction were examined in this study; hence this study used the wrong study design
Ueshima 1988	Effects of alcohol reduction were examined in this study; hence this study used the wrong study design

Study	Reason for exclusion
Ueshima 1993	Effects of alcohol reduction were examined in this study; hence this study used the wrong study design
Uhart 2010	This study was not placebo-controlled; hence this study used the wrong study design
Urquiaga 2015	This study used the wrong intervention because red wine grape pomace flour (WGPF) was given as the main intervention instead of alcohol
vanMierlo 2010	This study used the wrong study design. The intervention duration was 2 weeks, and measurements were made at the end of the study, which was not considered an acute effect. In addition, this study used the wrong intervention because polyphenol-rich solids were used as the main intervention instead of alcohol
Vatsalya 2011	Full text was not available for this study, and contact information for study authors was not found
Vazquez-Fresno 2012	This study used the wrong study design. The intervention duration was 28 days, and measurements were made at the end of the study, which was not considered an acute effect
Vena 2018a	Alcohol was combined with oxytocin; hence this study used the wrong intervention
Vena 2018b	Alcohol was combined with oxytocin; hence this study used the wrong intervention
Wensing 2006	This study used the wrong intervention because the combined effect of alcohol and vardenafil was examined instead of the effect of alcohol alone
Wilson 2014	This study used the wrong study design as intervention duration was 6 months, which was not considered an acute effect of alcohol
Witkowska 2017	This study used the wrong intervention because it examined the effect of red wine polyphenols rather than the effect of alcohol
Woerdeman 2018	Red wine polyphenol was used as the intervention instead of alcohol; hence this study used the wrong intervention
Wray 2013	Full text was not available for this study, and contact information of study authors was not found
Yang 2017	Alcohol consumption was self-reported in this study; hence this study used the wrong study design
YftachGepner 2015	This study used the wrong study design. The intervention duration was 6 months, and measurements were made at the end of the study, which was not considered an acute effect
Yin 2007	This study was questionnaire-based; hence this study used the wrong study design
Yin 2015	This study was questionnaire-based; hence this study used the wrong study design
Zamora-Ros 2006	This study was not placebo-controlled. Only red wine, white wine, ethanol as sparkling wine, and gin were compared in this study; hence this study used the wrong study design
Zheng 2012	This study was not placebo-controlled (compared traditional Chinese liquor and tea flavour liquor); hence this study used the wrong study design
Ziauddeen 2013	This study used the wrong intervention. Alcohol was combined with mu-opioid receptor antagonist GSK1521498
Zilkens 2003	Alcohol reduction was examined in this study; hence this study used the wrong study design

Study	Reason for exclusion
Zilkens 2005	This study used the wrong study design. The intervention duration was 4 weeks, and measurements were made on the last or second-last day of the study, which was not considered an acute effect

BPA: bisphenol A.
HFD: high-fat diet.
LBNP: lower body negative pressure.
MD: Mediterranean-type diet.
RGSE: red grape seed extract.
WGPF: wine grape pomace flour.

Characteristics of ongoing studies *[ordered by study ID]*

Polzein ongoing

Study name	Alcohol and Neural Cardiovascular Control in Binge Drinkers
Methods	Randomised, cross-over, double-blind, placebo-based
Participants	• Male and female binge drinkers (age 21 to 40 years) • Binge drinkers are defined by a pattern of consuming ≥ 4 drinks if female (≥ 5 drinks if males) in ≤ 2 hours on more than 1 occasion within the past 6 months, and at least once in the past 30 days • Women must be eumenorrhoeic and premenopausal with regular and consistent menstrual cycles (i.e. ~ 25 to 30 day ovarian/uterine cycles that include 2 to 7 days of menstruation)
Interventions	Intervention: alcohol Placebo: fluid control
Outcomes	Primary outcome measure • Sympathetic nerve activity Secondary outcome measure: baroreflex function • Baroreflex function (linear relationship between beat-to-beat blood pressure and sympathetic nerve activity) Other outcome measures: • Nocturnal blood pressure (change in blood pressure during sleep when compared to evening/morning wakefulness) • Sleep quality • Sympathetic reactivity
Starting date	21 May 2018
Contact information	Responsible party: Michigan Technological University Joanne Polzein (jpolzien@mtu.edu) Cheryl Gherna (cagherna@mtu.edu)
Notes	Status: recruiting Estimated study completion date: September 2022

DATA AND ANALYSES

Comparison 1. Low-dose alcohol vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Systolic blood pressure	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 ≤ 6 hours	2	56	Mean Difference (IV, Fixed, 95% CI)	-1.48 [-8.38, 5.42]
1.2 Diastolic blood pressure	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 ≤ 6 hours	2	56	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-6.91, 3.99]
1.3 Mean arterial blood pressure	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 ≤ 6 hours	2	56	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-4.55, 1.65]
1.4 Heart rate	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 ≤ 6 hours	2	56	Mean Difference (IV, Fixed, 95% CI)	5.06 [1.88, 8.24]

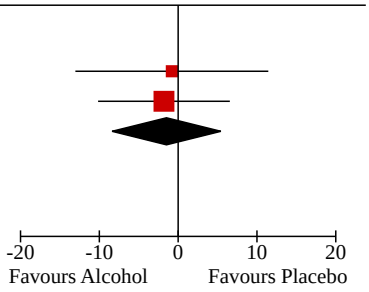
Analysis 1.1. Comparison 1: Low-dose alcohol vs placebo, Outcome 1: Systolic blood pressure

Study or Subgroup	MD	SE	Alcohol Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 ≤ 6 hours						
Cheyne 2004	0	6.2449	17	17	31.8%	-0.80 [-13.04 , 11.44]
Nishiwaki 2017	0	4.264	11	11	68.2%	-1.80 [-10.16 , 6.56]
Subtotal (95% CI)			**28**	**28**	**100.0%**	**-1.48 [-8.38 , 5.42]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%

Test for overall effect: Z = 0.42 (P = 0.67)

Test for subgroup differences: Not applicable

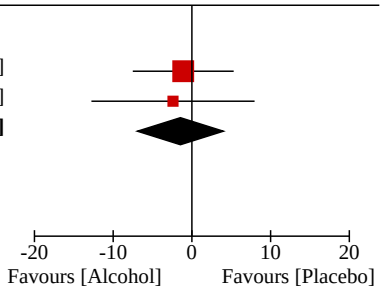


Analysis 1.2. Comparison 1: Low-dose alcohol vs placebo, Outcome 2: Diastolic blood pressure

Study or Subgroup	MD	SE	Alcohol Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 ≤ 6 hours						
Cheyne 2004	0	3.2696	17	17	72.3%	-1.10 [-7.51 , 5.31]
Nishiwaki 2017	0	5.2874	11	11	27.7%	-2.40 [-12.76 , 7.96]
Subtotal (95% CI)			**28**	**28**	**100.0%**	**-1.46 [-6.91 , 3.99]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.60)

Test for subgroup differences: Not applicable

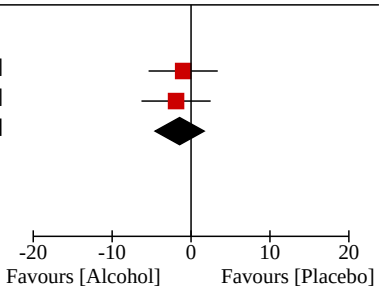


Analysis 1.3. Comparison 1: Low-dose alcohol vs placebo, Outcome 3: Mean arterial blood pressure

Study or Subgroup	MD	SE	Alcohol Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 ≤ 6 hours						
Cheyne 2004	0	2.2361	17	17	50.0%	-1.00 [-5.38 , 3.38]
Nishiwaki 2017	0	2.2361	11	11	50.0%	-1.90 [-6.28 , 2.48]
Subtotal (95% CI)			**28**	**28**	**100.0%**	**-1.45 [-4.55 , 1.65]**

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable

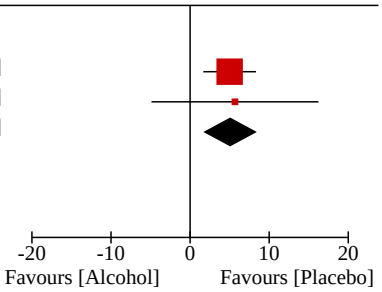


Analysis 1.4. Comparison 1: Low-dose alcohol vs placebo, Outcome 4: Heart rate

Study or Subgroup	MD	SE	Alcohol Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 ≤ 6 hours						
Cheyne 2004	0	1.7	17	17	90.9%	5.00 [1.67 , 8.33]
Nishiwaki 2017	0	5.3852	11	11	9.1%	5.67 [-4.88 , 16.22]
Subtotal (95% CI)			**28**	**28**	**100.0%**	**5.06 [1.88 , 8.24]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 3.12 (P = 0.002)

Test for subgroup differences: Not applicable



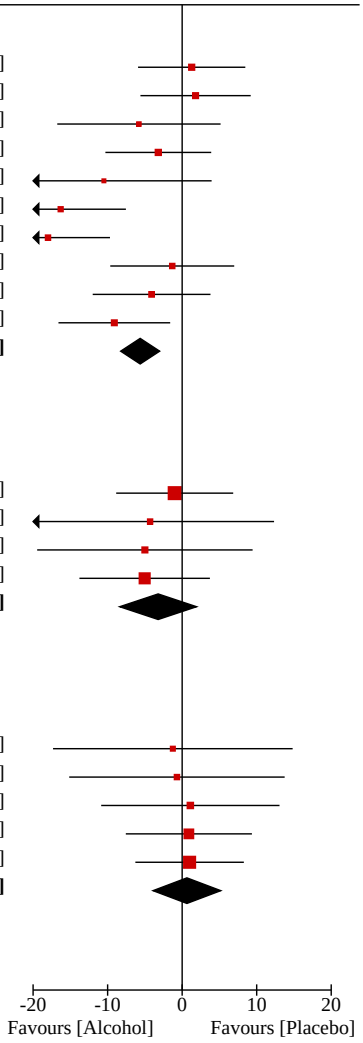
Comparison 2. Medium-dose alcohol vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Systolic blood pressure	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.1 ≤ 6 hours	9	260	Mean Difference (IV, Fixed, 95% CI)	-5.63 [-8.25, -3.02]
2.1.2 7 to 12 hours	4	108	Mean Difference (IV, Fixed, 95% CI)	-3.22 [-8.37, 1.93]
2.1.3 ≥ 13 hours	4	112	Mean Difference (IV, Fixed, 95% CI)	0.64 [-3.90, 5.18]
2.2 Diastolic blood pressure	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.2.1 ≤ 6 hours	9	260	Mean Difference (IV, Fixed, 95% CI)	-4.01 [-6.02, -2.00]
2.2.2 7 to 12 hours	4	108	Mean Difference (IV, Fixed, 95% CI)	-1.19 [-4.29, 1.90]
2.2.3 ≥ 13 hours	4	112	Mean Difference (IV, Fixed, 95% CI)	1.78 [-0.95, 4.51]
2.3 Mean arterial blood pressure	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 ≤ 6 hours	12	360	Mean Difference (IV, Random, 95% CI)	-2.92 [-5.76, -0.07]
2.3.2 7 to 12 hours	4	108	Mean Difference (IV, Random, 95% CI)	-2.11 [-4.69, 0.48]
2.3.3 ≥ 13 hours	4	112	Mean Difference (IV, Random, 95% CI)	1.43 [-1.18, 4.04]
2.4 Heart rate	12		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.4.1 ≤ 6 hours	12	344	Mean Difference (IV, Fixed, 95% CI)	4.62 [3.14, 6.11]
2.4.2 7 to 12 hours	4	108	Mean Difference (IV, Fixed, 95% CI)	1.22 [-1.88, 4.32]
2.4.3 ≥ 13 hours	3	72	Mean Difference (IV, Fixed, 95% CI)	1.37 [-2.12, 4.86]

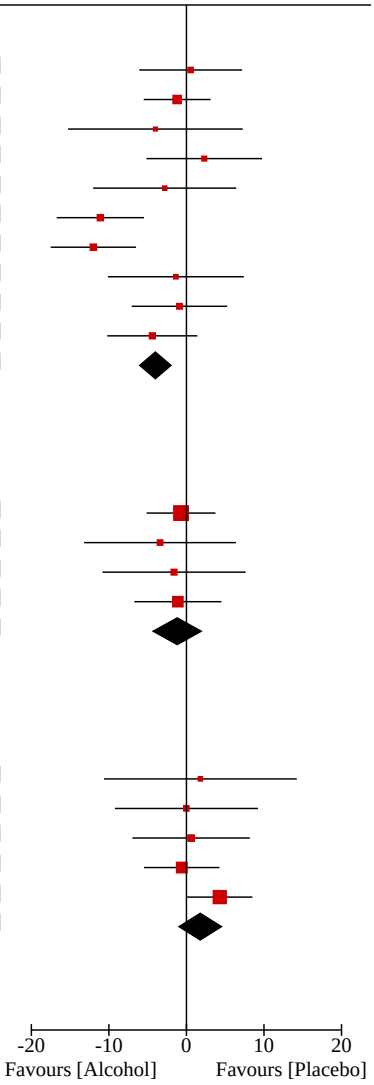
Analysis 2.1. Comparison 2: Medium-dose alcohol vs placebo, Outcome 1: Systolic blood pressure

Study or Subgroup	MD	SE	Experimental Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 ≤ 6 hours						
Chen 1986	0	3.6711	8	10	13.2%	1.28 [-5.92 , 8.48]
Fantin 2016	0	3.7739	18	18	12.5%	1.80 [-5.60 , 9.20]
Foppa 2002	0	5.5902	13	13	5.7%	-5.80 [-16.76 , 5.16]
Karatzi 2005	0	3.6216	15	15	13.6%	-3.20 [-10.30 , 3.90]
Kawano 1992	0	7.374	13	13	3.3%	-10.50 [-24.95 , 3.95]
Kawano 2000	0	4.4654	10	10	8.9%	-16.30 [-25.05 , -7.55]
Kojima 1993	0	4.2426	21	21	9.9%	-18.00 [-26.32 , -9.68]
Nishiwaki 2017	0	4.2426	11	11	9.9%	-1.33 [-9.65 , 6.99]
Rosito 1999	0	4.0311	10	10	10.9%	-4.10 [-12.00 , 3.80]
Rosito 1999	0	3.8237	10	10	12.2%	-9.10 [-16.59 , -1.61]
Subtotal (95% CI)			**129**	**131**	**100.0%**	**-5.63 [-8.25 , -3.02]**
Heterogeneity: Chi² = 24.51, df = 9 (P = 0.004); I² = 63%						
Test for overall effect: Z = 4.22 (P < 0.0001)						
2.1.2 7 to 12 hours						
Fantin 2016	0	4.005	18	18	43.1%	-1.00 [-8.85 , 6.85]
Foppa 2002	0	8.4853	13	13	9.6%	-4.30 [-20.93 , 12.33]
Kawano 1992	0	7.374	13	13	12.7%	-5.00 [-19.45 , 9.45]
Kawano 2000	0	4.4654	10	10	34.6%	-5.03 [-13.78 , 3.72]
Subtotal (95% CI)			**54**	**54**	**100.0%**	**-3.22 [-8.37 , 1.93]**
Heterogeneity: Chi² = 0.55, df = 3 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.23 (P = 0.22)						
2.1.3 ≥ 13 hours						
Foppa 2002	0	8.2006	13	13	8.0%	-1.25 [-17.32 , 14.82]
Kawano 1992	0	7.374	13	13	9.9%	-0.70 [-15.15 , 13.75]
Kawano 2000	0	6.1033	10	10	14.4%	1.10 [-10.86 , 13.06]
Rosito 1999	0	4.3161	10	10	28.8%	0.90 [-7.56 , 9.36]
Rosito 1999	0	3.713	10	10	38.9%	1.00 [-6.28 , 8.28]
Subtotal (95% CI)			**56**	**56**	**100.0%**	**0.64 [-3.90 , 5.18]**
Heterogeneity: Chi² = 0.10, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Chi² = 5.59, df = 2 (P = 0.06), I² = 64.2%						



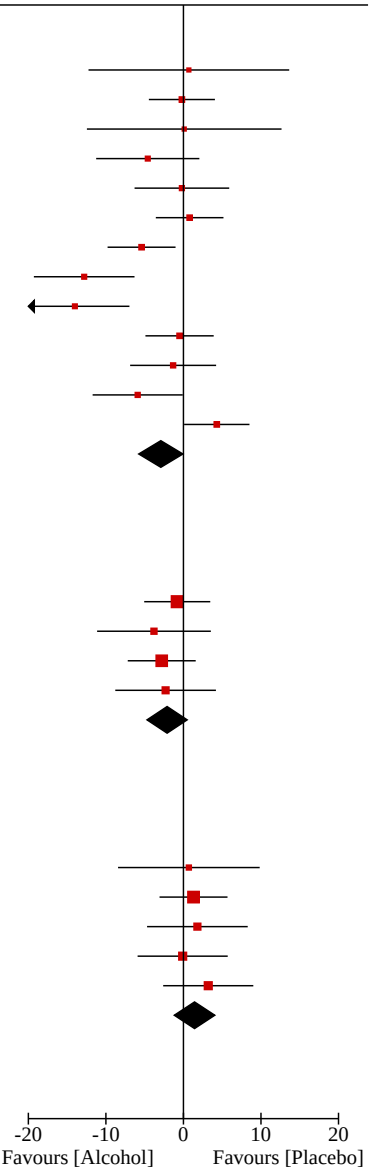
Analysis 2.2. Comparison 2: Medium-dose alcohol vs placebo, Outcome 2: Diastolic blood pressure

Study or Subgroup	MD	SE	Alcohol Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
2.2.1 ≤ 6 hours						
Chen 1986	0	3.3866	8	10	9.2%	0.55 [-6.09 , 7.19]
Fantin 2016	0	2.1976	18	18	21.8%	-1.20 [-5.51 , 3.11]
Foppa 2002	0	5.7454	13	13	3.2%	-4.00 [-15.26 , 7.26]
Karatzi 2005	0	3.8004	15	15	7.3%	2.30 [-5.15 , 9.75]
Kawano 1992	0	4.7068	13	13	4.7%	-2.80 [-12.03 , 6.43]
Kawano 2000	0	2.8714	10	10	12.7%	-11.10 [-16.73 , -5.47]
Kojima 1993	0	2.8083	21	21	13.3%	-12.00 [-17.50 , -6.50]
Nishiwaki 2017	0	4.4721	11	11	5.3%	-1.36 [-10.13 , 7.41]
Rosito 1999	0	3.142	10	10	10.6%	-0.90 [-7.06 , 5.26]
Rosito 1999	0	2.9666	10	10	11.9%	-4.40 [-10.21 , 1.41]
Subtotal (95% CI)			**129**	**131**	**100.0%**	**-4.01 [-6.02 , -2.00]**
Heterogeneity: Chi² = 21.81, df = 9 (P = 0.009); I² = 59%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
2.2.2 7 to 12 hours						
Fantin 2016	0	2.2689	18	18	48.4%	-0.70 [-5.15 , 3.75]
Foppa 2002	0	5	13	13	10.0%	-3.40 [-13.20 , 6.40]
Kawano 1992	0	4.7068	13	13	11.2%	-1.60 [-10.83 , 7.63]
Kawano 2000	0	2.8638	10	10	30.4%	-1.10 [-6.71 , 4.51]
Subtotal (95% CI)			**54**	**54**	**100.0%**	**-1.19 [-4.29 , 1.90]**
Heterogeneity: Chi² = 0.25, df = 3 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.76 (P = 0.45)						
2.2.3 ≥ 13 hours						
Foppa 2002	0	6.3411	13	13	4.8%	1.80 [-10.63 , 14.23]
Kawano 1992	0	4.7068	13	13	8.8%	0.00 [-9.23 , 9.23]
Kawano 2000	0	3.8643	10	10	13.0%	0.60 [-6.97 , 8.17]
Rosito 1999	0	2.4821	10	10	31.5%	-0.60 [-5.46 , 4.26]
Rosito 1999	0	2.1506	10	10	41.9%	4.30 [0.08 , 8.52]
Subtotal (95% CI)			**56**	**56**	**100.0%**	**1.78 [-0.95 , 4.51]**
Heterogeneity: Chi² = 2.53, df = 4 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
Test for subgroup differences: Chi² = 11.40, df = 2 (P = 0.003), I² = 82.4%						

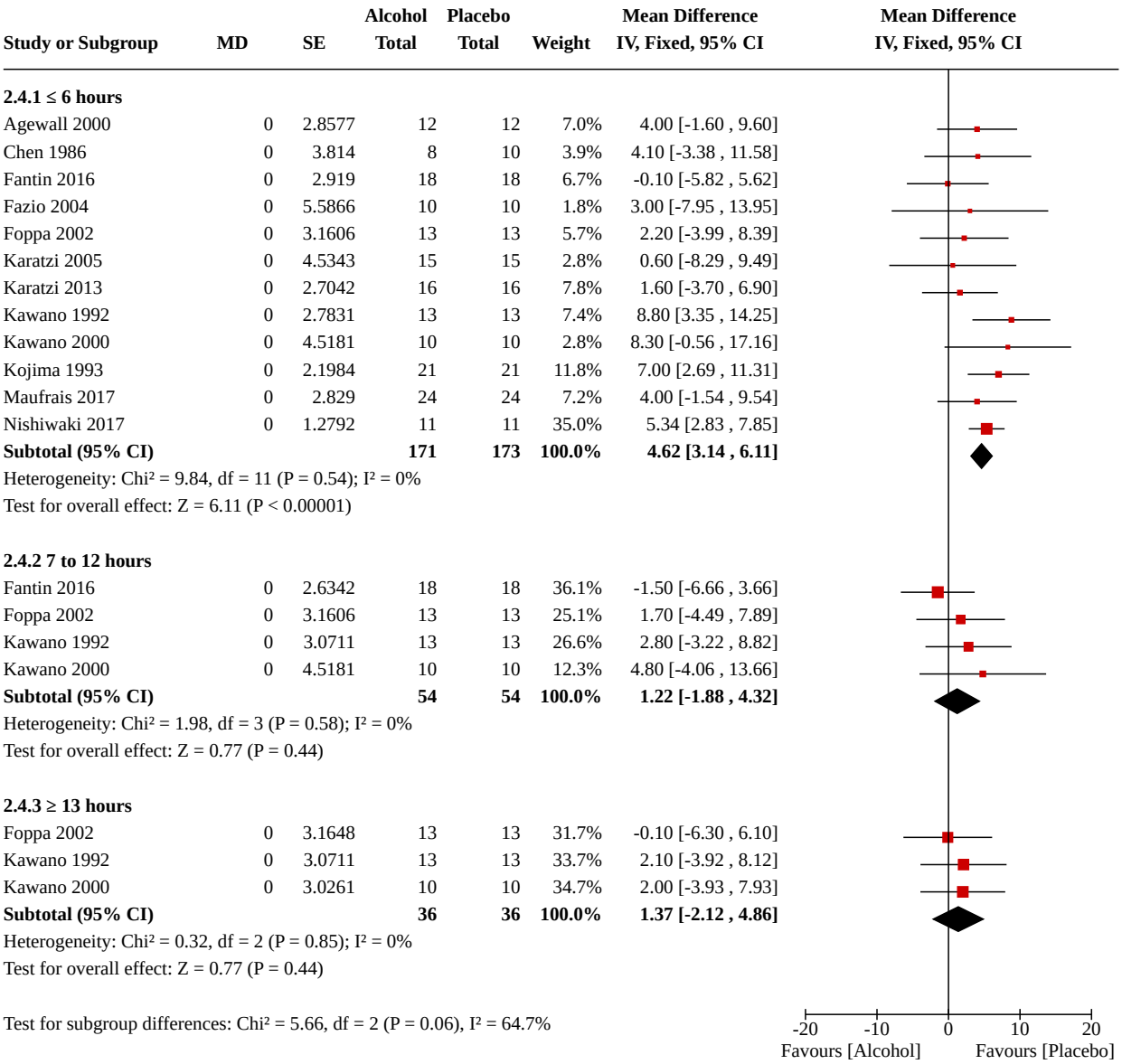


Analysis 2.3. Comparison 2: Medium-dose alcohol vs placebo, Outcome 3: Mean arterial blood pressure

Study or Subgroup	MD	SE	Alcohol Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 ≤ 6 hours						
Chen 1986	0	6.603	8	10	3.5%	0.70 [-12.24 , 13.64]
Fantin 2016	0	2.1731	18	18	9.5%	-0.20 [-4.46 , 4.06]
Fazio 2004	0	6.4031	10	10	3.6%	0.10 [-12.45 , 12.65]
Foppa 2002	0	3.3948	13	13	7.3%	-4.60 [-11.25 , 2.05]
Karatzi 2005	0	3.1145	15	15	7.8%	-0.20 [-6.30 , 5.90]
Karatzi 2013	0	2.2256	16	16	9.4%	0.80 [-3.56 , 5.16]
Kawano 1992	0	2.2361	13	13	9.4%	-5.40 [-9.78 , -1.02]
Kawano 2000	0	3.3112	10	10	7.4%	-12.80 [-19.29 , -6.31]
Kojima 1993	0	3.589	21	21	6.9%	-14.00 [-21.03 , -6.97]
Maufrais 2017	0	2.2457	24	24	9.4%	-0.50 [-4.90 , 3.90]
Nishiwaki 2017	0	2.8284	11	11	8.3%	-1.33 [-6.87 , 4.21]
Rosito 1999	0	2.965	10	10	8.0%	-5.90 [-11.71 , -0.09]
Rosito 1999	0	2.1506	10	10	9.5%	4.30 [0.08 , 8.52]
Subtotal (95% CI)			**179**	**181**	**100.0%**	**-2.92 [-5.76 , -0.07]**
Heterogeneity: Tau² = 17.47; Chi² = 38.36, df = 12 (P = 0.0001); I² = 69%						
Test for overall effect: Z = 2.01 (P = 0.04)						
2.3.2 7 to 12 hours						
Fantin 2016	0	2.1731	18	18	36.9%	-0.80 [-5.06 , 3.46]
Foppa 2002	0	3.7417	13	13	12.4%	-3.80 [-11.13 , 3.53]
Kawano 1992	0	2.2361	13	13	34.8%	-2.80 [-7.18 , 1.58]
Kawano 2000	0	3.3112	10	10	15.9%	-2.30 [-8.79 , 4.19]
Subtotal (95% CI)			**54**	**54**	**100.0%**	**-2.11 [-4.69 , 0.48]**
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
2.3.3 ≥ 13 hours						
Foppa 2002	0	4.6594	13	13	8.2%	0.70 [-8.43 , 9.83]
Kawano 1992	0	2.2361	13	13	35.4%	1.30 [-3.08 , 5.68]
Kawano 2000	0	3.3112	10	10	16.1%	1.80 [-4.69 , 8.29]
Rosito 1999	0	2.965	10	10	20.1%	-0.10 [-5.91 , 5.71]
Rosito 1999	0	2.965	10	10	20.1%	3.20 [-2.61 , 9.01]
Subtotal (95% CI)			**56**	**56**	**100.0%**	**1.43 [-1.18 , 4.04]**
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 4 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Test for subgroup differences: Chi² = 5.77, df = 2 (P = 0.06), I² = 65.3%						



Analysis 2.4. Comparison 2: Medium-dose alcohol vs placebo, Outcome 4: Heart rate



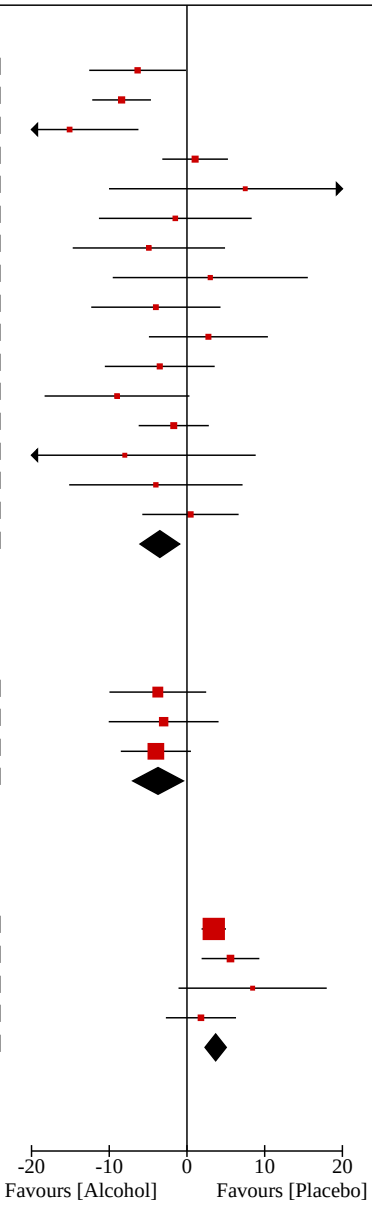
Comparison 3. High-dose alcohol vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Systolic blood pressure	16		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1.1 ≤ 6 hours	16	620	Mean Difference (IV, Random, 95% CI)	-3.49 [-6.03, -0.95]
3.1.2 7 to 12 hours	3	88	Mean Difference (IV, Random, 95% CI)	-3.72 [-6.97, -0.48]
3.1.3 ≥ 13 hours	4	188	Mean Difference (IV, Random, 95% CI)	3.69 [2.33, 5.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Diastolic blood pressure	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.2.1 ≤ 6 hours	14	532	Mean Difference (IV, Random, 95% CI)	-1.91 [-3.86, 0.04]
3.2.2 7 to 12 hours	3	88	Mean Difference (IV, Random, 95% CI)	-1.71 [-4.59, 1.17]
3.2.3 ≥ 13 hours	4	188	Mean Difference (IV, Random, 95% CI)	2.37 [0.25, 4.49]
3.3 Mean arterial blood pressure	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.3.1 ≤ 6 hours	17	640	Mean Difference (IV, Random, 95% CI)	-1.53 [-3.34, 0.28]
3.3.2 7 to 12 hours	3	88	Mean Difference (IV, Random, 95% CI)	-2.47 [-5.69, 0.75]
3.3.3 ≥ 13 hours	4	188	Mean Difference (IV, Random, 95% CI)	2.96 [0.35, 5.58]
3.4 Heart rate	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.4.1 ≤ 6 hours	17	704	Mean Difference (IV, Random, 95% CI)	5.75 [3.99, 7.51]
3.4.2 7 to 12 hours	5	198	Mean Difference (IV, Random, 95% CI)	6.16 [3.04, 9.28]
3.4.3 ≥ 13 hours	6	298	Mean Difference (IV, Random, 95% CI)	2.70 [0.80, 4.60]

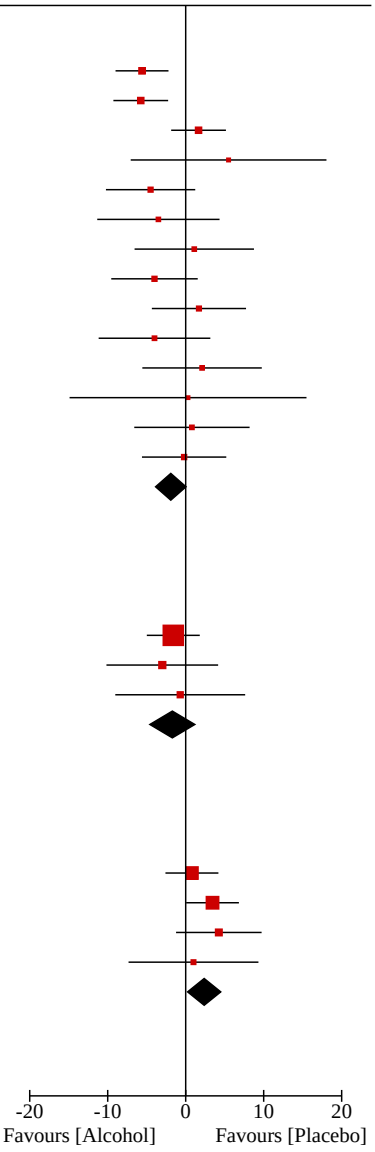
Analysis 3.1. Comparison 3: High-dose alcohol vs placebo, Outcome 1: Systolic blood pressure

Study or Subgroup	MD	SE	Alcohol Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 ≤ 6 hours						
Barden 2013	0	3.1754	24	24	8.1%	-6.35 [-12.57 , -0.13]
Bau 2005	0	1.9267	50	50	11.7%	-8.41 [-12.19 , -4.63]
Buckman 2015	0	4.5185	24	24	5.4%	-15.10 [-23.96 , -6.24]
Dai 2002	0	2.1537	40	40	11.0%	1.05 [-3.17 , 5.27]
Hering 2011	0	8.9443	24	24	1.9%	7.50 [-10.03 , 25.03]
Koenig 1997	0	5.0133	15	15	4.7%	-1.50 [-11.33 , 8.33]
Mahmud 2002	0	5	8	8	4.7%	-4.90 [-14.70 , 4.90]
Maule 1993	0	6.4031	10	10	3.3%	3.00 [-9.55 , 15.55]
Narkiewicz 2000	0	4.2426	14	14	5.9%	-4.00 [-12.32 , 4.32]
Potter 1986	0	3.9051	16	16	6.5%	2.76 [-4.89 , 10.41]
Rosito 1999	0	3.6057	10	10	7.1%	-3.50 [-10.57 , 3.57]
Rossinen 1997	0	4.7539	20	20	5.1%	-9.00 [-18.32 , 0.32]
Stott 1987	0	2.3022	10	10	10.6%	-1.70 [-6.21 , 2.81]
Stott 1991	0	8.594	8	8	2.0%	-8.00 [-24.84 , 8.84]
Williams 2004	0	5.6907	13	13	3.9%	-4.00 [-15.15 , 7.15]
Zeichner 1985	0	3.161	24	24	8.2%	0.45 [-5.75 , 6.65]
Subtotal (95% CI)			**310**	**310**	**100.0%**	**-3.49 [-6.03 , -0.95]**
Heterogeneity: Tau² = 10.63; Chi² = 27.51, df = 15 (P = 0.02); I² = 45%						
Test for overall effect: Z = 2.69 (P = 0.007)						
3.1.2 7 to 12 hours						
Barden 2013	0	3.1754	24	24	27.2%	-3.75 [-9.97 , 2.47]
Rosito 1999	0	3.6057	10	10	21.1%	-3.00 [-10.07 , 4.07]
Stott 1987	0	2.3022	10	10	51.7%	-4.00 [-8.51 , 0.51]
Subtotal (95% CI)			**44**	**44**	**100.0%**	**-3.72 [-6.97 , -0.48]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 2.25 (P = 0.02)						
3.1.3 ≥ 13 hours						
Barden 2013	0	0.8	24	24	75.4%	3.45 [1.88 , 5.02]
Bau 2005	0	1.8953	50	50	13.4%	5.60 [1.89 , 9.31]
Rosito 1999	0	4.8648	10	10	2.0%	8.45 [-1.08 , 17.98]
Stott 1987	0	2.3022	10	10	9.1%	1.80 [-2.71 , 6.31]
Subtotal (95% CI)			**94**	**94**	**100.0%**	**3.69 [2.33 , 5.05]**
Heterogeneity: Tau² = 0.00; Chi² = 2.74, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 5.31 (P < 0.00001)						
Test for subgroup differences: Chi² = 34.64, df = 2 (P < 0.00001), I² = 94.2%						



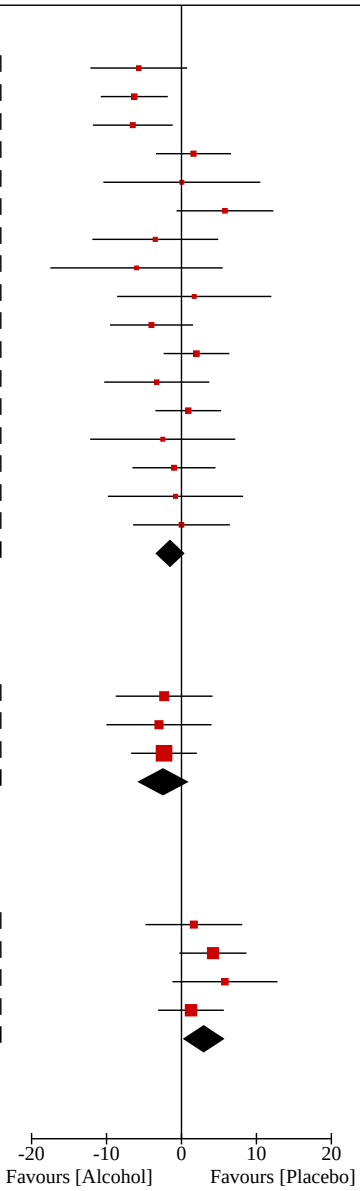
Analysis 3.2. Comparison 3: High-dose alcohol vs placebo, Outcome 2: Diastolic blood pressure

Study or Subgroup	MD	SE	Alcohol Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
3.2.1 ≤ 6 hours						
Barden 2013	0	1.7321	24	24	13.4%	-5.60 [-8.99 , -2.21]
Bau 2005	0	1.7907	50	50	13.0%	-5.76 [-9.27 , -2.25]
Dai 2002	0	1.7907	40	40	13.0%	1.65 [-1.86 , 5.16]
Hering 2011	0	6.4031	24	24	2.2%	5.50 [-7.05 , 18.05]
Koenig 1997	0	2.9212	15	15	7.7%	-4.50 [-10.23 , 1.23]
Mahmud 2002	0	4	8	8	4.9%	-3.50 [-11.34 , 4.34]
Maule 1993	0	3.9051	10	10	5.0%	1.10 [-6.55 , 8.75]
Narkiewicz 2000	0	2.8284	14	14	8.0%	-4.00 [-9.54 , 1.54]
Potter 1986	0	3.0806	16	16	7.1%	1.70 [-4.34 , 7.74]
Rosito 1999	0	3.6531	10	10	5.6%	-4.00 [-11.16 , 3.16]
Stott 1987	0	3.9072	10	10	5.0%	2.10 [-5.56 , 9.76]
Stott 1991	0	7.75	8	8	1.5%	0.30 [-14.89 , 15.49]
Williams 2004	0	3.7724	13	13	5.3%	0.80 [-6.59 , 8.19]
Zeichner 1985	0	2.7576	24	24	8.2%	-0.20 [-5.60 , 5.20]
Subtotal (95% CI)			**266**	**266**	**100.0%**	**-1.91 [-3.86 , 0.04]**
Heterogeneity: Tau² = 4.38; Chi² = 20.03, df = 13 (P = 0.09); I² = 35%						
Test for overall effect: Z = 1.92 (P = 0.05)						
3.2.2 7 to 12 hours						
Barden 2013	0	1.7321	24	24	71.9%	-1.59 [-4.98 , 1.80]
Rosito 1999	0	3.6531	10	10	16.2%	-3.00 [-10.16 , 4.16]
Stott 1987	0	4.2485	10	10	11.9%	-0.70 [-9.03 , 7.63]
Subtotal (95% CI)			**44**	**44**	**100.0%**	**-1.71 [-4.59 , 1.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 2 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
3.2.3 ≥ 13 hours						
Barden 2013	0	1.7321	24	24	39.1%	0.80 [-2.59 , 4.19]
Bau 2005	0	1.7255	50	50	39.4%	3.44 [0.06 , 6.82]
Rosito 1999	0	2.7973	10	10	15.0%	4.25 [-1.23 , 9.73]
Stott 1987	0	4.2485	10	10	6.5%	1.00 [-7.33 , 9.33]
Subtotal (95% CI)			**94**	**94**	**100.0%**	**2.37 [0.25 , 4.49]**
Heterogeneity: Tau² = 0.00; Chi² = 1.76, df = 3 (P = 0.62); I² = 0%						
Test for overall effect: Z = 2.19 (P = 0.03)						
Test for subgroup differences: Chi² = 9.62, df = 2 (P = 0.008), I² = 79.2%						



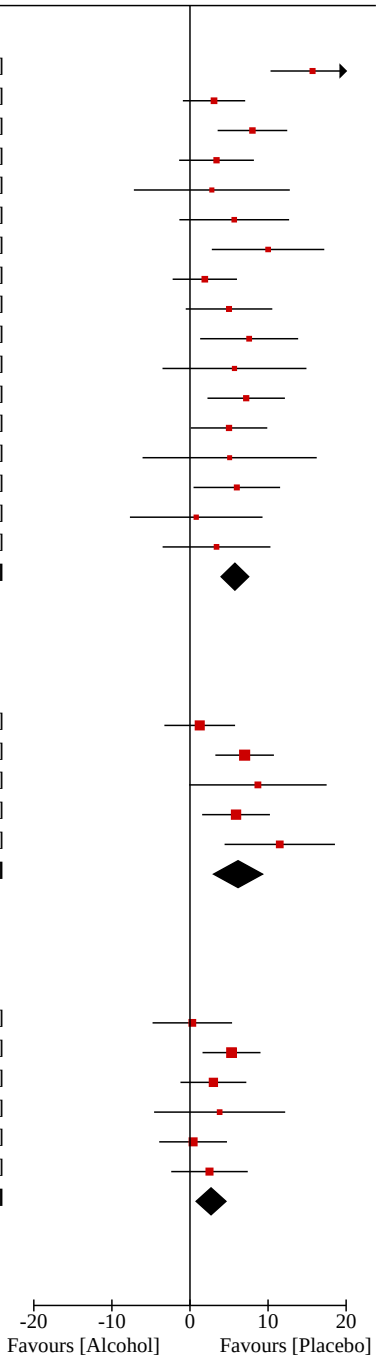
Analysis 3.3. Comparison 3: High-dose alcohol vs placebo, Outcome 3: Mean arterial blood pressure

Study or Subgroup	MD	SE	Experimental Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.3.1 ≤ 6 hours						
Barden 2013	0	3.2946	24	24	5.8%	-5.70 [-12.16 , 0.76]
Bau 2005	0	2.2825	50	50	9.5%	-6.30 [-10.77 , -1.83]
Buckman 2015	0	2.718	24	24	7.7%	-6.50 [-11.83 , -1.17]
Dai 2002	0	2.552	40	40	8.3%	1.60 [-3.40 , 6.60]
Dumont 2010	0	5.3452	14	14	2.6%	0.05 [-10.43 , 10.53]
Hering 2011	0	3.2946	24	24	5.8%	5.80 [-0.66 , 12.26]
Koenig 1997	0	4.2849	15	15	3.9%	-3.50 [-11.90 , 4.90]
Mahmud 2002	0	5.8673	8	8	2.2%	-6.00 [-17.50 , 5.50]
Maule 1993	0	5.2479	10	10	2.7%	1.70 [-8.59 , 11.99]
Narkiewicz 2000	0	2.8284	14	14	7.3%	-4.00 [-9.54 , 1.54]
Potter 1986	0	2.2361	16	16	9.7%	2.00 [-2.38 , 6.38]
Rosito 1999	0	3.5777	10	10	5.2%	-3.30 [-10.31 , 3.71]
Stott 1987	0	2.2361	10	10	9.7%	0.90 [-3.48 , 5.28]
Stott 1991	0	4.9406	8	8	3.0%	-2.50 [-12.18 , 7.18]
Van De Borne 1997	0	2.8284	16	16	7.3%	-1.00 [-6.54 , 4.54]
Williams 2004	0	4.6027	13	13	3.4%	-0.80 [-9.82 , 8.22]
Zeichner 1985	0	3.2946	24	24	5.8%	0.00 [-6.46 , 6.46]
Subtotal (95% CI)			**320**	**320**	**100.0%**	**-1.53 [-3.34 , 0.28]**
Heterogeneity: Tau² = 3.77; Chi² = 22.02, df = 16 (P = 0.14); I² = 27%						
Test for overall effect: Z = 1.66 (P = 0.10)						
3.3.2 7 to 12 hours						
Barden 2013	0	3.2946	24	24	24.9%	-2.31 [-8.77 , 4.15]
Rosito 1999	0	3.5777	10	10	21.1%	-3.00 [-10.01 , 4.01]
Stott 1987	0	2.2361	10	10	54.0%	-2.33 [-6.71 , 2.05]
Subtotal (95% CI)			**44**	**44**	**100.0%**	**-2.47 [-5.69 , 0.75]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 2 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.50 (P = 0.13)						
3.3.3 ≥ 13 hours						
Barden 2013	0	3.2946	24	24	16.4%	1.65 [-4.81 , 8.11]
Bau 2005	0	2.2825	50	50	34.1%	4.20 [-0.27 , 8.67]
Rosito 1999	0	3.5777	10	10	13.9%	5.80 [-1.21 , 12.81]
Stott 1987	0	2.2361	10	10	35.6%	1.27 [-3.11 , 5.65]
Subtotal (95% CI)			**94**	**94**	**100.0%**	**2.96 [0.35 , 5.58]**
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 3 (P = 0.65); I² = 0%						
Test for overall effect: Z = 2.22 (P = 0.03)						
Test for subgroup differences: Chi² = 9.42, df = 2 (P = 0.009), I² = 78.8%						



Analysis 3.4. Comparison 3: High-dose alcohol vs placebo, Outcome 4: Heart rate

Study or Subgroup	MD	SE	Alcohol Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.4.1 ≤ 6 hours						
Barden 2013	0	2.7462	24	24	6.7%	15.70 [10.32 , 21.08]
Bau 2005	0	2.036	50	50	9.4%	3.08 [-0.91 , 7.07]
Bau 2011	0	2.2741	35	35	8.4%	8.00 [3.54 , 12.46]
Buckman 2015	0	2.4417	24	24	7.7%	3.40 [-1.39 , 8.19]
Dai 2002	0	5.0946	40	40	2.7%	2.80 [-7.19 , 12.79]
Dumont 2010	0	3.5857	14	14	4.7%	5.67 [-1.36 , 12.70]
Hering 2011	0	3.6742	24	24	4.5%	10.00 [2.80 , 17.20]
Maule 1993	0	2.1019	10	10	9.1%	1.90 [-2.22 , 6.02]
Narkiewicz 2000	0	2.8284	14	14	6.5%	5.00 [-0.54 , 10.54]
Potter 1986	0	3.2016	16	16	5.5%	7.58 [1.30 , 13.86]
Rosito 1999	0	4.7029	10	10	3.0%	5.70 [-3.52 , 14.92]
Rossinen 1997	0	2.5298	20	20	7.4%	7.20 [2.24 , 12.16]
Stott 1987	0	2.5	10	10	7.5%	5.00 [0.10 , 9.90]
Stott 1991	0	5.691	8	8	2.2%	5.08 [-6.07 , 16.23]
Van De Borne 1997	0	2.8284	16	16	6.5%	6.00 [0.46 , 11.54]
Williams 2004	0	4.3323	13	13	3.5%	0.80 [-7.69 , 9.29]
Zeichner 1985	0	3.5225	24	24	4.8%	3.40 [-3.50 , 10.30]
Subtotal (95% CI)			**352**	**352**	**100.0%**	**5.75 [3.99 , 7.51]**
Heterogeneity: Tau² = 4.46; Chi² = 24.35, df = 16 (P = 0.08); I² = 34%						
Test for overall effect: Z = 6.41 (P < 0.00001)						
3.4.2 7 to 12 hours						
Barden 2013	0	2.3094	24	24	23.6%	1.25 [-3.28 , 5.78]
Bau 2011	0	1.9124	35	35	28.0%	7.00 [3.25 , 10.75]
Rosito 1999	0	4.4905	10	10	9.9%	8.70 [-0.10 , 17.50]
Rossinen 1997	0	2.2136	20	20	24.6%	5.90 [1.56 , 10.24]
Stott 1987	0	3.6056	10	10	13.8%	11.50 [4.43 , 18.57]
Subtotal (95% CI)			**99**	**99**	**100.0%**	**6.16 [3.04 , 9.28]**
Heterogeneity: Tau² = 5.41; Chi² = 7.19, df = 4 (P = 0.13); I² = 44%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
3.4.3 ≥ 13 hours						
Barden 2013	0	2.5981	24	24	14.0%	0.30 [-4.79 , 5.39]
Bau 2005	0	1.8937	50	50	26.3%	5.32 [1.61 , 9.03]
Bau 2011	0	2.1514	35	35	20.4%	3.00 [-1.22 , 7.22]
Rosito 1999	0	4.2826	10	10	5.1%	3.80 [-4.59 , 12.19]
Rossinen 1997	0	2.2136	20	20	19.2%	0.40 [-3.94 , 4.74]
Stott 1987	0	2.5	10	10	15.1%	2.50 [-2.40 , 7.40]
Subtotal (95% CI)			**149**	**149**	**100.0%**	**2.70 [0.80 , 4.60]**
Heterogeneity: Tau² = 0.00; Chi² = 3.94, df = 5 (P = 0.56); I² = 0%						
Test for overall effect: Z = 2.78 (P = 0.005)						
Test for subgroup differences: Chi² = 6.44, df = 2 (P = 0.04), I² = 69.0%						



ADDITIONAL TABLES

Table 1. Baseline characteristics

Study ID	Randomised participants, N	Mean age (range)	Mean body weight, kg	Health condition	Reported dose of alcohol	Duration of intervention	Baseline SBP (SD)	Baseline DBP (SD)	Baseline HR (SD)
Agewall 2000	12	31 (younger than 40 years old)	Not reported	Healthy, normotensive non-smokers	31.25 g	10 minutes	121 (6)	79 (4)	61 (7)
Barden 2013	24	56 (20 to 65)	Not reported	Healthy	41 g	30 minutes	115 (11)	72 (6)	62 (7)
Bau 2005	100	20.7 (18 to 25)	Not reported	Healthy non-smokers	60 g	30 minutes	114.2	64.8	72.43 (10.9)
Bau 2011	70	20.7 (18 to 25)	Not reported	Healthy	60 g	30 minutes	Not reported	Not reported	75 (10)
Buckman 2015	72	21.5	Not reported	Healthy	0.90 mL/kg for men 0.78 mL/kg for women	15 minutes	116.9 (13.5)	Not reported	66.9 (9.9)
Chen 1986	20	19 to 32	Not reported	Healthy, normotensive non-smokers	Target to achieve blood level of 0.05%	Not reported (mentioned that fairly fast rate)	118 (12.88)	62.25 (5.1)	63.13 (7.1)
Cheyne 2004	17	35 (21 to 46)	Not reported	Type 1 diabetes	0.35 mg/kg BW	Not reported	116.2 (18.7)	66.8 (8.2)	70 (12)
Dai 2002	40	19 to 25 years	81.35	Healthy	0.5 g/kg	5 minutes	114.1	72.6	63.5
Dumont 2010	14	22.1 (18 to 29)	Not reported	Regular user of MDMA, otherwise healthy	Target blood alcohol level 0.6%, equivalent of 2 to 3 alcoholic beverages.	3 hours to maintain target BAC	Not reported	Not reported	66

Table 1. Baseline characteristics *(Continued)*

Fantin 2016	18	34.2 (25 to 53)	70.2 (53 to 85.6)	Healthy	30 g	10 hours	110.3 (12)	80 (8)	75.5 (11.5)
Fazio 2004	10	22 (20 to 25)	Not reported	Healthy	0.3 g/kg	5 minutes	Not reported	Not reported	68
Foppa 2002	13	55 (43 to 65)	Not reported	Hypertensive and centrally obese	23 g	15 minutes	130	83	72 (8.72)
Hering 2011	24	44	Not reported	13 hypertensive and 11 normotensive	1 g/kg	20 minutes	Hypertensive: 150 (21) Normotensive: 136 (13.2)	Hypertensive: 91 (14.4) Normotensive: 76 (10)	Hypertensive: 72 (7.2) Normotensive: 70 (10)
Karatzi 2005	15	52.4	Not reported	Coronary artery disease	30 g	Not reported	109.8 (9.2)	80.7 (10.8)	67.1 (13.1)
Karatzi 2013	16	28.5	77.5	Healthy non-smokers	20 g	15 minutes	115.4 (6.2)	68.5 (5.4)	60 (8.1)
Kawano 1992	13	55.2 (22 to 70)	65.2	Mild to moderate essential hypertension	51 g	Not reported	159 (18.8)	91.3 (12)	61.5
Kawano 2000	10	54 (32 to 67)	70 (60 to 78)	Mild essential hypertension	55.3 g (1 mL/kg BW)	60 minutes	147	91	65
Koenig 1997	15	20 to 35	76	Healthy	10 mL/kg BW	30 minutes	127 (11)	80 (9.5)	Not reported
Kojima 1993	21	56.5 (33 to 73)	Not reported	Essential hypertension	1 mL/kg BW	30 minutes	146 (18.33)	89 (9.2)	59 (9.2)
Mahmud 2002	8	21 to 40	70	Healthy, normotensive non-smokers	56 g (0.8 g/kg of BW)	10 minutes	93.3 (10)	67 (8)	Not reported
Maufrais 2017	24	23.3	62.9	Healthy	0.4 g/kg	5 minutes	Not reported	Not reported	69 (9.8)

Table 1. Baseline characteristics *(Continued)*

Maule 1993	10	31 (22 to 51)	68.1 (50 to 81)	Healthy	34 g (0.5 g/kg BW)	10 minutes	122	70	62 (6.3)
Narkiewicz 2000	19	26	Not reported	Healthy	1 g/kg BW	30 minutes	111 (11.2)	61 (7.5)	57 (7.5)
Nishiwaki 2017	11	21.1 (20 to 22)	62.6	Healthy non-smokers	11 g and 19.25 g	5 minutes	123 (6.63)	71 (6.63)	59 (9.94)
Potter 1986	16	22 (20 to 30)	77	Healthy, normotensive	0.75 g/kg	15 minutes	122.5 (11)	72.5 (9)	63.2 (8)
Rosito 1999	40	22.2 (19 to 30)	Not reported	Healthy	60 g	1 hour	124.2 (10.7)	76.2 (9.4)	70.5 (12.6)
Rossinen 1997	20	39 to 68	Not reported	Coronary artery disease and myocardial ischaemia Patients were taking usual medicine	1.25 g/kg	1 hour 30 minutes	132 (16)	Not reported	69.5
Stott 1987	10	18 to 31	56 to 101	Healthy	1.3 g/kg	1 hour	115.5	67	70.5
Stott 1991	8	81 (70 to 96)	68.4	Normotensive	0.5 g/kg	15 minutes	130 (18.3)	77.5 (15.5)	57 (7.5)
Van De Borne 1997	16	26	Not reported	Healthy	1 g/kg	30 minutes	Not reported	Not reported	59 (8)
Williams 2004	13	59 (48 to 70)	86	Coronary artery disease	0.52 g/kg	20 minutes	135 (11)	82 (7)	55 (11)
Zeichner 1985	48	20.9 (19 to 23)	Not reported	Healthy	1 g/kg	20 minutes	115.5 (10.2)	70.4 (9.1)	69.4 (12.10)

BAC: blood alcohol concentration.
BW: body weight.
DBP: diastolic blood pressure.
HR: heart rate.
SBP: systolic blood pressure.
SD: standard deviation.

Table 2. Contact with corresponding authors

Study ID	Reason for contact	Contacted? (Yes/No)	Response? (Yes/No)
Agewall 2000	Method of allocation concealment used in RCT was not mentioned	No Comment - contact information cannot be found	NA
Bau 2005	Method of allocation concealment used in RCT was not mentioned	Yes	No
Bau 2011	Method of allocation concealment used in RCT was not mentioned	Yes	No
Buckman 2015	Method of allocation concealment used in RCT was not mentioned	Yes	Yes
Chen 1986	Methods of randomisation and allocation concealment used in RCT were not mentioned	No Comment - contact information cannot be found	NA
Dai 2002	Method of allocation concealment used in RCT was not mentioned	Yes	No
Dumont 2010	Methods of randomisation and allocation concealment, blinding of participants and personnel, and blinding of outcome assessment used in RCT were not mentioned	Yes	No
Fantin 2016	Methods of randomisation and allocation concealment used in RCT were not mentioned	Yes	No
Fazio 2004	Methods of randomisation and allocation concealment used in RCT were not mentioned	Yes	No
Foppa 2002	Methods of randomisation and allocation concealment used in RCT were not mentioned	Yes	Yes
Hering 2011	Methods of allocation concealment used in RCT was not mentioned	Yes	Yes
Karatzi 2005	Methods of randomisation and allocation concealment, blinding of participants and personnel, and blinding of outcome assessment used in RCT were not mentioned	Yes	No
Karatzi 2013	Methods of randomisation and allocation concealment used in RCT were not mentioned	Yes	No
Kawano 1992	Methods of randomisation and allocation concealment used in RCT were not mentioned	Yes Comment - contact information cannot be found in the study. However, we used contact infor-	No

Table 2. Contact with corresponding authors *(Continued)*

		mation provided in Kawano 2000	
Kawano 2000	Methods of randomisation and allocation concealment used in RCT were not mentioned	Yes	No
Kojima 1993	Methods of randomisation and allocation concealment used in RCT were not mentioned	No Comment - contact information cannot be found	NA
Mahmud 2002	Methods of randomisation and allocation concealment, blinding of participants and personnel, and blinding of outcome assessment used in RCT were not mentioned	Yes	No
Maufrais 2017	Method of allocation concealment used in RCT was not mentioned	Yes	No
Maule 1993	Methods of randomisation and allocation concealment used in RCT were not mentioned	No Comment - contact information cannot be found	NA
Narkiewicz 2000	Methods of randomisation and allocation concealment used in RCT were not mentioned	Yes	No
Nishiwaki 2017	Methods of randomisation and allocation concealment used in RCT were not mentioned	Yes	No
Potter 1986	Methods of randomisation and allocation concealment and blinding of outcome assessor used in RCT were not mentioned	No Comment - contact information cannot be found	NA
Rossinen 1997	Methods of randomisation and allocation concealment used in RCT were not mentioned	No Comment - contact information cannot be found	NA
Rosito 1999	Methods of randomisation and allocation concealment and blinding of participants and personnel used in RCT were not mentioned	Yes	Yes
Stott 1987	Methods of randomisation and allocation concealment used in RCT were not mentioned	No Comment - contact information cannot be found	NA
Stott 1991	Methods of randomisation and allocation concealment used in RCT were not mentioned	No Comment - contact information cannot be found	NA

Table 2. Contact with corresponding authors *(Continued)*

Van De Borne 1997	Methods of randomisation and allocation concealment used in RCT were not mentioned	No Comment - contact information cannot be found	NA
Williams 2004	Methods of randomisation and allocation concealment used in RCT were not mentioned	No Comment - contact information cannot be found	NA
Zeichner 1985	Methods of randomisation and allocation concealment used in RCT were not mentioned	No Comment - contact information cannot be found	NA

NA: not applicable.
RCT: randomised controlled trial.

Table 3. Sensitivity analysis: fixed-effect model vs random-effects model

Outcomes or subgroup	Mean difference, IV, fixed-effect model, 95% CI	Mean difference, IV, random-effects model, 95% CI
2.1 SBP (≤ 6 hours)	-5.63 [-8.25, -3.02] Heterogeneity: Chi^2 = 24.51, df = 9 (P = 0.004); I^2 = 63% Test for overall effect: Z = 4.22 (P < 0.0001)	-6.15 [-10.55, -1.75] Heterogeneity: Chi^2 = 24.51, df = 9 (P = 0.004); I^2 = 63% Test for overall effect: Z = 2.74 (P = 0.006)
2.2 DBP (≤ 6 hours)	-4.01 [-6.02, -2.00] Heterogeneity: Chi^2 = 21.81, df = 9 (P = 0.009); I^2 = 59% Test for overall effect: Z = 3.91 (P < 0.0001)	-3.76 [-7.02, -0.50] Heterogeneity: Chi^2 = 21.81, df = 9 (P = 0.009); I^2 = 59% Test for overall effect: Z = 2.26 (P = 0.02)
2.3 MAP (≤ 6 hours)	-2.17 [-3.68, -0.65] Heterogeneity: Chi^2 = 38.36, df = 12 (P = 0.0001); I^2 = 69% Test for overall effect: Z = 2.80 (P = 0.005)	-2.92 [-5.76, -0.07] Heterogeneity: Chi^2 = 38.36, df = 12 (P = 0.0001); I^2 = 69% Test for overall effect: Z = 2.01 (P = 0.04)

CI: confidence interval.
DBP: diastolic blood pressure.
IV: inverse variance.
MAP: mean arterial pressure.
SBP: systolic blood pressure.

Table 4. Sensitivity analysis: blinded studies vs unblinded studies

Outcomes or subgroups	Blinded studies, mean difference, IV, fixed-effect model, 95% CI	Unblinded, mean difference, IV, fixed-effect model, 95% CI

Table 4. Sensitivity analysis: blinded studies vs unblinded studies *(Continued)*

2.1 SBP (< 6 hours)	-4.56 [-8.39, -0.73] Heterogeneity: Chi² = 2.14, df = 3 (P = 0.54); I² = 0% Test for overall effect: Z = 2.33 (P = 0.02)	-6.57 [-10.15, -3.00] Heterogeneity: Chi² = 21.80, df = 5 (P = 0.0006); I² = 77% Test for overall effect: Z = 3.60 (P = 0.0003)
2.2 DBP (< 6 hours)	-1.50 [-4.89, 1.89] Heterogeneity: Chi² = 1.99, df = 3 (P = 0.57); I² = 0% Test for overall effect: Z = 0.86 (P = 0.39)	-5.37 [-7.86, -2.87] Heterogeneity: Chi² = 16.57, df = 5 (P = 0.005); I² = 70% Test for overall effect: Z = 4.22 (P < 0.0001)
2.3 MAP (< 6 hours)	-0.11 [-3.39, 3.18] Heterogeneity: Chi² = 8.24, df = 4 (P = 0.08); I² = 51% Test for overall effect: Z = 0.06 (P = 0.95)	-4.93 [-8.83, -1.02] Heterogeneity: Chi² = 21.61, df = 7 (P = 0.003); I² = 68% Test for overall effect: Z = 2.47 (P = 0.01)
2.4 HR (< 6 hours)	4.35 [2.31, 6.40] Heterogeneity: Chi² = 2.33, df = 3 (P = 0.51); I² = 0% Test for overall effect: Z = 4.17 (P < 0.0001)	4.92 [2.77, 7.08] Heterogeneity: Chi² = 7.37, df = 7 (P = 0.39); I² = 5% Test for overall effect: Z = 4.48 (P < 0.00001)
3.1 SBP (< 6 hours)	-3.80 [-8.03, 0.43] Heterogeneity: Chi² = 21.01, df = 7 (P = 0.004); I² = 67% Test for overall effect: Z = 1.76 (P = 0.08)	-2.84 [-5.53, -0.14] Heterogeneity: Chi² = 6.04, df = 7 (P = 0.54); I² = 0% Test for overall effect: Z = 2.06 (P = 0.04)
3.2 DBP (< 6 hours)	-1.88 [-4.73, 0.97] Heterogeneity: Tau² = 6.68; Chi² = 11.57, df = 6 (P = 0.07); I² = 48% Test for overall effect: Z = 1.29 (P = 0.20)	-1.99 [-4.89, 0.90] Heterogeneity: Tau² = 3.87; Chi² = 8.16, df = 6 (P = 0.23); I² = 26% Test for overall effect: Z = 1.35 (P = 0.18)
3.3 MAP (< 6 hours)	-1.62 [-3.98, 0.74] Heterogeneity: Chi² = 10.45, df = 8 (P = 0.23); I² = 23% Test for overall effect: Z = 1.35 (P = 0.18)	-1.44 [-4.46, 1.57] Heterogeneity: Chi² = 11.54, df = 7 (P = 0.12); I² = 39% Test for overall effect: Z = 0.94 (P = 0.35)
3.4 HR (< 6 hours)	4.82 [3.01, 6.63] Heterogeneity: Chi² = 5.79, df = 8 (P = 0.67); I² = 0% Test for overall effect: Z = 5.22 (P < 0.00001)	6.62 [3.21, 10.03] Heterogeneity: Chi² = 16.68, df = 7 (P = 0.02); I² = 58% Test for overall effect: Z = 3.81 (P = 0.0001)

CI: confidence interval.
DBP: diastolic blood pressure.
HR: heart rate.
IV: inverse variance.
MAP: mean arterial pressure.
SBP: systolic blood pressure.

Table 5. Differences between older and younger participants

Analysis	Older participants (mean age ≥ 50), **mean difference, IV, fixed-effect model, 95% CI**	Younger participants (mean age < 50), **mean difference, IV, fixed-effect model, 95% CI**
2.1 SBP (< 6 hours)	-11.25 [-15.63, -6.87] Test for overall effect: Z = 5.04 (P < 0.00001); df = 3 (P = 0.03); I^2 = 66%	-2.52 [-5.78, 0.74] Test for overall effect: Z = 1.52 (P = 0.13); df = 5 (P = 0.31); I^2 = 16%
2.2 DBP (<6 hours)	-7.82 [-11.08, -4.57] Test for overall effect: Z = 4.71 (P < 0.00001); df = 3 (P = 0.008); I^2 = 74%	-1.66 [-4.22, 0.89] Test for overall effect: Z = 1.28 (P = 0.20); df = 5 (P = 0.91); I^2 = 0%
3.1 SBP (<6 hours)	-6.71 [-11.23, -2.18] Test for overall effect: Z = 2.91 (P = 0.004); df = 3 (P = 0.92); I^2 = 0%	-3.04 [-4.87, -1.20]; Test for overall effect: Z = 3.24 (P = 0.001); df = 11 (P = 0.010); I^2 = 56%
3.2 DBP (<6 hours)	-4.30 [-7.32, -1.27] Test for overall effect: Z = 2.78 (P = 0.005); df = 2 (P = 0.25); I^2 = 27%	-1.67 [-3.33, -0.01] Test for overall effect: Z = 1.97 (P = 0.05); df = 10 (P = 0.13); I^2 = 34%

CI: confidence interval.
DBP: diastolic blood pressure.
IV: inverse variance.
SBP: systolic blood pressure.

Table 6. Comparison between very high-dose alcohol and lower high-dose alcohol

Outcomes	**Very high dose (≥ 60 g)** **Mean difference, IV, fixed-effect model, 95% CI**	**Lower high dose (31 to 59 g)** **Mean difference, IV, fixed-effect model, 95% CI**
3.1. SBP	-5.12 [-7.32, -2.92] Test for overall effect: Z = 4.57 (P < 0.00001); df = 7 (P = 0.02); I^2 = 56%	-1.20 [-3.90, 1.49] Test for overall effect: Z = 0.88 (P = 0.38); df = 7 (P = 0.47); I^2 = 0%
3.2. DBP	-3.21 [-5.49, -0.92] Test for overall effect: Z = 2.75 (P = 0.006); df = 5 (P = 0.22); I^2 = 29%	-1.65 [-3.53, 0.23] Test for overall effect: Z = 1.72 (P = 0.09); df = 7 (P = 0.10); I^2 = 41%
3.3. MAP	2.17 [-4.09, -0.25] Test for overall effect: Z = 2.21 (P = 0.03); df = 7 (P = 0.04); I^2 = 52%	-0.47 [-2.83, 1.90] Test for overall effect: Z = 0.39 (P = 0.70); df = 8 (P = 0.63); I^2 = 0%
3.4. HR	5.43 [3.76, 7.11] Test for overall effect: Z = 6.35 (P < 0.00001); df = 9 (P = 0.76); I^2 = 0%	6.09 [3.67, 8.51] Test for overall effect: Z = 4.93 (P < 0.00001); df = 6 (P = 0.005); I^2 = 67%

CI: confidence interval.
DBP: diastolic blood pressure.
HR: heart rate.
IV: inverse variance.
MAP: mean arterial pressure.
SBP: systolic blood pressure.

APPENDICES

Appendix 1. Search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily, and Versions(R) <1946 to July 13, 2018>
Search Date: 14 July 2018
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1 exp alcohol drinking/
2 (alcohol$ or beer? or liquor? or spirit? or wine?).tw,kf.
3 or/1-2
4 cardiovascular.mp.
5 hypertension/
6 hypertens$.tw,kf.
7 exp blood pressure/
8 (blood pressure or bp or dbp or sbp).mp.
9 exp heart rate/
10 ((heart or pulse) adj2 rate?).tw,kf.
11 or/4-10
12 randomized controlled trial.pt.
13 controlled clinical trial.pt.
14 randomized.ab.
15 placebo.ab.
16 clinical trials as topic/
17 randomly.ab.
18 trial.ti.
19 or/12-18
20 animals/ not (humans/ and animals/)
21 19 not 20
22 3 and 11 and 21

Database: Cochrane Hypertension Specialised Register via Cochrane Register of Studies (CRS-Web)
Search Date: 15 July 2018

#1 MESH DESCRIPTOR Alcohol Drinking EXPLODE ALL AND INSEGMENT
#2 (alcohol* OR beer* OR liquor* OR spirit* OR wine) AND INSEGMENT
#3 #1 OR #2 AND INSEGMENT
#4 RCT:DE AND INSEGMENT
#5 Review:ODE AND INSEGMENT
#6 #4 OR #5 AND INSEGMENT
#7 #3 AND #6 AND INSEGMENT

Database: Cochrane Central Register of Controlled Trials via Cochrane Register of Studies (CRS-Web)
Search Date: 14 July 2018

#1 MESH DESCRIPTOR Alcohol Drinking EXPLODE ALL AND CENTRAL:TARGET
#2 (alcohol* OR beer* OR liquor* OR spirit* OR wine) NEAR5 (consum* OR drink* OR usage OR use*):ti,ab AND CENTRAL:TARGET
#3 #1 OR #2 AND CENTRAL:TARGET
#4 cardiovascular AND CENTRAL:TARGET
#5 MESH DESCRIPTOR Hypertension AND CENTRAL:TARGET
#6 hypertens* AND CENTRAL:TARGET
#7 MESH DESCRIPTOR Blood Pressure EXPLODE ALL AND CENTRAL:TARGET
#8 (blood pressure OR bp OR dbp OR sbp) AND CENTRAL:TARGET
#9 MESH DESCRIPTOR Heart Rate EXPLODE ALL AND CENTRAL:TARGET
#10 (heart OR pulse) NEAR2 rate* AND CENTRAL:TARGET
#11 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 AND CENTRAL:TARGET
#12 #3 AND #11 AND CENTRAL:TARGET

Database: Embase <1974 to 2018 July 13>
Search Date: 14 July 2018
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1 drinking behavior/ (46148)
2 ((alcohol$ or beer? or liquor? or spirit? or wine?) adj10 (consum$ or drink$ or usage or use?)).tw.
3 or/1-2 (172470)
4 cardiovascular.tw. (553583)
5 hypertens$.tw. (579052)
6 exp blood pressure/ (524780)
7 (blood pressure or bp or dbp or sbp).tw.
8 exp heart rate/
9 ((heart or pulse) adj2 rate?).tw.
10 or/4-9
11 randomized controlled trial/
12 crossover procedure/
13 double-blind procedure/
14 (randomi?ed or randomly).tw.
15 (crossover$ or cross-over$).tw.
16 placebo.ab.
17 (doubl$ adj blind$).tw.
18 assign$.ab.
19 allocat$.ab.
20 or/11-19
21 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
22 20 not 21
23 3 and 10 and 22

Database: ClinicalTrials.gov
Search Date: 15 July 2018

Other terms: randomized
Intervention/treatment: alcohol OR beer OR liquor OR spirits OR wine
Study type: Interventional Studies (Clinical Trials)
Outcome Measures: blood pressure OR heart rate

Database: WHO International Clinical Trials Registry Platform (ICTRP)
Search Date: 15 July 2018

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randomized AND blood pressure AND alcohol
randomized AND blood pressure AND beer
randomized AND blood pressure AND liquor
randomized AND blood pressure AND spirits
randomized AND blood pressure AND wine
randomized AND heart rate AND alcohol
randomized AND heart rate AND beer
randomized AND heart rate AND liquor
randomized AND heart rate AND spirits
randomized AND heart rate AND wine

HISTORY

Protocol first published: Issue 9, 2017
Review first published: Issue 7, 2020

CONTRIBUTIONS OF AUTHORS

James M Wright (JMW) formulated the idea, developed the basis of the protocol, and contributed to data analysis, interpretation of the final result, and editing of the final draft of the review.

Sara Tasnim (ST) and Chantel Tang (CT) drafted the protocol with help from JMW. Both ST and CT independently assessed studies for inclusion or exclusion and assessed the risk of bias of all included studies.

ST extracted data, checked data entry, conducted data analysis, interpreted study results, and drafted the final review.

CT checked data entry and contributed to drafting of the review.

Vijaya Musini (VM) contributed to data analysis, interpretation of the final result, and editing of the final draft of the review.

All review authors reviewed and approved the final version.

DECLARATIONS OF INTEREST

Chantel Tang: none known.

Sara Tasnim: none known.

Vijaya Musini: none known.

James M Wright: none known.

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- Department of Anesthesiology, Pharmacology & Therapeutics, University of BC, Canada

  infrastructure

External sources

- British Columbia Ministry of Health, Canada

  Therapeutics Initiative grant

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

According to the published protocol, we intended to include only double-blind RCTs in this review. Because higher doses of alcohol exert specific pharmacological effects on drinkers, we had a few double-blind RCTs after the first screening. Considering the difficulty of masking in these types of studies, we decided to also include single-blind and open-label studies in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Alcohol Drinking; *Alcoholic Beverages; Bias; Blood Pressure [*drug effects]; Central Nervous System Depressants [administration & dosage] [*pharmacology]; Cross-Over Studies; Ethanol [administration & dosage] [*pharmacology]; Heart Rate [*drug effects]; Randomized Controlled Trials as Topic; Sex Factors; Time Factors

MeSH check words

Adult; Aged; Aged, 80 and over; Female; Humans; Male; Middle Aged; Young Adult