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Tasnim S, Tang C, Wright JM.
Effect of alcohol on blood pressure.
*Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD012787.
DOI: 10.1002/14651858.CD012787.

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## TABLE OF CONTENTS

[Intervention Protocol]

# Effect of alcohol on blood pressure

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**Editorial group:** Cochrane Hypertension Group.
**Publication status and date:** New, published in Issue 9, 2017.

**Citation:** Tasnim S, Tang C, Wright JM. Effect of alcohol on blood pressure. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD012787. DOI: 10.1002/14651858.CD012787.



## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

**Primary objectives**

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

## BACKGROUND

### Description of the condition

Hypertension, or elevated blood pressure, is commonly defined as resting systolic blood (SBP) pressure above 140 mmHg or a diastolic blood pressure (DBP) above 90 mmHg - or both - assuming that the person is not taking any antihypertensive medication (Poulter 2015). Sustained hypertension is associated with an increased risk of stroke, myocardial infarction, heart failure, renal failure (Kannel 1972). Hypertension is one of the most common conditions seen with increasing age, affecting up to 31% of the world's adult population (Mills 2016). In this review, we will be looking at the effect of alcohol on blood pressure in people with both normal and elevated blood pressure.

### Description of the intervention

Alcohol has been a part of almost every human culture for a very long time (McGovern 2009). Many people use it for medicinal purposes because of its hypnotic/sedative and analgesic effects (Immonen 2011; Williams 1980). Also, an inverse relationship between light to moderate alcohol consumption and total mortality was reported in a meta-analysis (Di Castelnuovo 2006). However, the abuse of alcohol 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 (Seitz 2007; Kushi 2012). The World Health Organization (WHO) estimated that in 2012 around 3.3 million deaths worldwide were caused by alcohol abuse (WHO 2014).

### How the intervention might work

Alcohol can elevate blood pressure by a variety of mechanisms. Acute alcohol consumption affects the renin-angiotensin-aldosterone system (RAAS) by increasing plasma renin activity (Puddey 1985). The 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 and also stimulates aldosterone secretion from the adrenal gland, which increases sodium and water retention (Schrier 1999). As a result, peripheral resistance and blood volume increases leading to elevated arterial blood pressure in both healthy and hypertensive people.

Another possible mechanism may concern the increase in plasma cortisol levels that follows heavy alcohol consumption (Jenkins 1968). Several studies have suggested a role for cortisol in alcohol-induced hypertension (Potter 1986; Husain,2014).

Alcohol has also been reported to diminish baroreceptor sensitivity, which is a key factor in regulating blood pressure (Abdel-Rahman 1985; Rupp 1996). Baroreceptors are mechanoreceptors that can sense the changes in blood pressure and maintain blood pressure by controlling heart rate, contractility and peripheral resistance.

### Why it is important to do this review

There are many observational studies that show an association between moderate consumption of alcohol and a reduced incidence of adverse cardiovascular effects (Worm 2013). Although numerous reports suggest that alcohol intake - particularly in larger amounts - is associated with elevated blood pressure, currently, there is no systematic review of double-blind, randomized controlled trials that documents the short-term effect of alcohol on blood pressure. This proposed systematic review will provide useful information about the dose-related magnitude and time course of the effect of alcohol on blood pressure in people with both normal and elevated blood pressure.

## OBJECTIVES

### Primary objectives

To determine the short-term dose-related effect 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 the short-term dose-related effect 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

Studies must be double-blinded, randomized, placebo-controlled, parallel or cross-over trials (both phases) in healthy or hypertensive adults comparing the short-term effect of different doses of alcohol on blood pressure and heart rate. Trials must report blood pressure after short-term exposure to alcohol (maximum duration, 4 weeks).

#### Types of participants

Healthy or hypertensive adults aged 18 years or older with no exclusions.

#### Types of interventions

Intervention: different doses in grams of any type of ethanol-based beverage. In multi-arm trials we will include the arms studying different doses of ethanol.

Control: similar tasting beverage with no ethanol content.

#### Types of outcome measures

##### Primary outcomes

Change in early (1 to 6 hours after consumption), intermediate (6 to 12 hours after consumption) and late (13 hours to 26 hours after consumption) resting seated systolic and diastolic blood pressure.

##### Secondary outcomes

Change in resting heart rate at the same time intervals as blood pressure outcomes above.

## Search methods for identification of studies

### Electronic searches

The Cochrane Hypertension Information Specialist will search the following databases from date of inception for published, unpublished, and ongoing studies:

- the Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web);
- the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web);
- MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations;
- Embase Ovid (from 1974 onwards);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (www.who.it.trialsearch).

The subject strategies for databases will be modelled on the search strategy designed for MEDLINE in Appendix 1. Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomized controlled (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### Searching other resources

- The Hypertension Information Specialist will search the Hypertension Specialised Register segment (which includes searches of MEDLINE and Epistemonikos for systematic reviews) to retrieve published systematic reviews related to this review title, so that we can scan their reference lists to identify additional relevant trials.
- We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.
- We will contact experts/organizations in the field to obtain additional information on relevant trials.
- We may contact trial authors for clarification and further data if trial reports are unclear.

## Data collection and analysis

### Selection of studies

ST and CT will perform the initial search of all the databases to identify citations with potential relevance, and will exclude articles whose titles or abstracts, or both are clearly irrelevant with an initial screen. The full text of the remaining articles will be retrieved and translated into English where required. The references and abstracts identified by our search will be imported into Covidence. Two reviewers (ST and CT) will assess the eligibility of the trials independently using a trial selection form based on the criteria listed above. The third reviewer (JMW) will resolve discrepancies, if necessary. The reasons for exclusion will be provided in the Characteristics of excluded studies table for all the full text reports that are retrieved and excluded. A PRISMA flow chart will be produced to describe the flow of selection of studies.

### Data extraction and management

Two review authors (ST and CT) will perform data extraction independently using a standard data collection form, followed by a cross-check. In the case of disagreement, a third party (JMW) will be involved to resolve the disagreement. If necessary, we will contact the authors of the studies for information about unclear study designs. We will extract the following data where reported:

- participants: age, gender, ethnicity, health background;
- intervention: type of alcoholic beverage, dosage, duration of the trial;
- control: placebo (similar tasting beverage with no alcohol);
- outcome: blood pressure and heart rate at different times after consumption in any settings and units;
- study design: double-blinded, randomized controlled trials (parallel or cross-over design).

All extracted data will be imported and double-checked in RevMan 5.

### Assessment of risk of bias in included studies

Two review authors (ST and CT) will independently assess the risk of bias following the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* chapter 8 (Higgins 2011), for the following domains:

- 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); and
- other potential sources of bias.

The review authors (ST and CT) will classify each domain as being at a low, high or uncertain risk of bias. In the case of disagreement, a third party (JMW) will be involved in order to discuss and resolve the disagreement.

### Measures of treatment effect

All the outcomes for this review (blood pressure and heart rate) produce continuous data. We will calculate and report mean difference (MD), with 95% confidence interval (95% CI).

### Unit of analysis issues

Both phases of cross-over trials could lead to some unit of analysis issues. We will deal with these as described in the *Cochrane Handbook for Systematic Reviews of Interventions* and only pool them with the other trials if appropriate and using generic inverse variance. N values will be adjusted to avoid double-counting of participants in both phases of cross-over trials. The effect of cross-over trial will be tested by doing a sensitivity analysis excluding them. In the case of multi-arm trials the placebo group will be divided by the number of arms to avoid double counting.

### Dealing with missing data

#### General missing data

We will contact the investigators of the studies via email, telephone call, letter or fax to request missing data (Higgins 2011. If investigators of the studies do not respond the study may be excluded.

#### Missing statistics

If a standard error (SE) is given instead of a standard deviation (SD), we will use the formula SD = SE x square root of n to calculate the SD.
If a 95% CI is given instead of a SD, we will calculate the SD using the guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* chapter 16 (Higgins 2011).
If SDs are missing for the change in blood pressure, we will impute the SD, based on information in the same study or from other studies that also have been using ethanol as an intervention to test blood pressure. We will use the following hierarchy (listed from highest to lowest) (Musini 2014) to impute SD values:

- 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 effect of alcohol.

### Assessment of heterogeneity

Standard chi-square test will be done by Review Manager Software 5.3 to test the heterogeneity. P value of 0.1 or less will be considered as statistical significant heterogeneity. Furthermore, $I^2$ will be used to interpret the level of heterogeneity based on the guide as described in *CoChrane Handbook for Systematic Reviews of Interventions* chapter 9 (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

### Assessment of reporting biases

Funnel plots will be used if there is minimum of 10 studies that contribute to a meta-analysis in order to detect the risk of reporting bias based on the symmetry of the plot (Higgins 2011).
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 of funnel plots. Therefore we will perform sensitivity analyses and search for unpublished studies as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* chapter 10 (Higgins 2011)

### Data synthesis

We will combine effect sizes across studies using the fixed-effect model unless there is substantial statistical heterogeneity between effect sizes. Where there is substantial and unexplained heterogeneity, we will pool data using the random-effects model. Where trials compare more than one dose of alcohol, each comparison will be handled separately. Participants in the control group will be divided by the number of groups in order to avoid double counting. Throughout, we will use 95% confidence intervals. In addition, sensitivity analysis based on different level of bias domain will be done to address differences in risk of bias in the analyses.

### Subgroup analysis and investigation of heterogeneity

If possible, we will perform subgroup analysis for:

- normotensive participants (defined as SBP < 140 mmHg and DBP < 90 mmHg) versus hypertensive participants (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg);
- gender.

### Sensitivity analysis

We will test the robustness of the results by performing several sensitivity analysis including:

- trials with low risk of bias versus high risk of bias.
- trials with reported SDs versus imputed SDs of blood pressure and heart rate change.

If possible, we will compare the fixed-effect model to random-effects model to test the impact of heterogeneity.

### 'Summary of findings' tables

We will use the GRADE approach to assess the quality 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 will use GRADEpro software ( GRADEpro 2014) to construct a 'Summary of findings' table to compare outcomes including change in SBP and DBP and heart rate. In addition, we will also include illustrative risks to present findings for the most important outcome (change in systolic blood pressure)

## ACKNOWLEDGEMENTS

We would like to acknowledge Douglas Salzwedel for designing the search strategy. We would also like to thank Dr Aaron Tejani and Dr Vijaya Musini for their advice and the Cochrane Hypertension Group for their help.

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* *Indicates the major publication for the study*

# APPENDICES

## Appendix 1. MEDLINE search strategy

### Database: Ovid MEDLINE(R) 1946 to present with Daily Update

---

1 exp alcohol drinking/
2 (alcohol$ or beer? or liquor? or spirit? or wine?).tw,kw.
3 or/1-2
4 exp blood pressure/
5 (blood pressure or bp or dbp or sbp).mp.
6 exp heart rate/
7 ((heart or pulse) adj2 rate?).tw,kw.
8 or/4-7
9 randomized controlled trial.pt.
10 controlled clinical trial.pt.

11 randomized.ab.
12 placebo.ab.
13 clinical trials as topic/
14 randomly.ab.
15 trial.ti.
16 or/9-15
17 animals/ not (humans/ and animals/)
18 16 not 17
19 3 and 8 and 18
20 remove duplicates from 19

## CONTRIBUTIONS OF AUTHORS

James M Wright formulated the idea and developed the basis of the protocol.

Sara Tasnim and Chantel Tang drafted the protocol with the help from James Wright. All the authors reviewed and approved the final protocol.

## DECLARATIONS OF INTEREST

Chantel Tang: none known

Sara Tasnim: none known

James M Wright: none known

## SOURCES OF SUPPORT


### Internal sources

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

### External sources

- No sources of support supplied