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Supplementary appendix

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Supplementary webappendix

For “The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis of trial data” by

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eText 1. Population impact methods

Modelling the distribution of blood pressure: The “belly curve”

In order to estimate the change in blood pressure distribution^{FN1} among populations, a new distribution was designed as an alternative to a simple normal distribution. A normal distribution does not adequately fit the distribution of blood pressure in European societies, as it underestimates the higher prevalence and the longer tail on the right hand side compared to the left hand side (for examples of blood pressure distributions; ¹⁻⁸). This distribution which we refer to as the “belly curve” is an attempt to model the asymmetric distribution of blood pressure as shown in representative studies for the general population (¹⁻⁸; see also ⁹).

The belly curve was designed according to the following rules about its shape:

- 1) The shape of the belly curve is made up of one half of a normal distribution to the right and left of its modus.
- 2) The standard deviation of the normal distribution making up the right half of the belly curve is twice that of the other.
- 3) The two normal distribution halves are multiplied by constants so as to yield a continuous distribution.

Based on these assumptions, it is possible to reverse engineer the required normal distributions if the overall mean and standard deviation of the final belly curve are known, therefore it is possible to obtain a belly curve fitting the mean and standard deviations found in surveys or other data.

The standard deviation of the normal distribution on the left of the modus of the belly curve σ_{left} , the modus of the belly curve, the mean of the of the belly curve, μ , and the standard deviation of the belly curve, σ_{belly} , are linked through the following expressions:

$$Modus = \mu - \sqrt{\frac{2}{\pi}} \cdot \sigma_{left}$$

$$\sigma_{belly}^2 = \mu^2 + Modus^2 + 2 \cdot Modus \cdot \sqrt{\frac{2}{\pi}} \cdot \sigma_{left} + 3 \cdot \sigma_{left}^2 - 2 \cdot \mu \cdot \left(Modus + \sqrt{\frac{2}{\pi}} \cdot \sigma_{left} \right)$$

We validated the curve by reproducing the actual distributions of blood pressure among people in the general population as well as among people with hypertension (controlled and uncontrolled) in Finland,^{1,2} Germany,⁵ Spain^{3,6,7} and the UK.⁸

Modelling the effects of interventions

The above expressions allow us to derive a belly curve for any given mean and standard deviation. To estimate the effects of interventions, 1 000 000 samples are created from the belly curve and a proportional decrease in blood pressure is applied to a subset of the samples, as given by the percentage of people with hypertension receiving the respective intervention.

Overall, two steps are required for a comparison of the current status with an alternative scenario where 50% of the people with problematic drinking (e.g., as defined by the AUDIT) receive additional interventions modelled as the average intervention in the randomized clinical trials described in the main text:

- 1) An initial belly curve was created using the current known mean and standard deviation of high blood pressure among people with hypertension (in our case this was based on the sex and age-specific means and standard deviations from the Health Survey of England 2014¹⁰).
- 2) The effect of the intervention for problem drinking was assessed by decreasing blood pressure of a randomly sampled subset of the belly distribution from step 1. The subset was chosen to reflect the prevalence of people with drinking levels of more than 24 grams pure alcohol, multiplied by the coverage

¹ For this article, we restricted ourselves to modelling systolic blood pressure, but the methodology can be used to model either systolic or diastolic blood pressure in the general population in European countries. It has also been validated to model these distributions in hypertensive populations.

rate. The size of the sex- and level of alcohol consumption-specific decrease was modelled based on the meta-analysis described in the main text.

As indicated above, our analysis assumes a coverage rate of alcohol interventions by 50%. We chose this potential coverage rate of 50% as this is the current intervention rate for depression in Europe or North America¹¹; depression is the most common mental disorder with similar levels of stigmatization as problematic alcohol use.

Modelling the effect of the changed distribution of blood pressure on cardiovascular diseases

To estimate the amount of deaths avoided with the intervention described here, we have to compare the blood pressure distributions before and after the intervention.

Conservatively, it is further assumed, that people with a systolic blood pressure below 140 mm Hg have a relative risk of 1.

In the case where the blood pressure distributions are known before and after the interventions, the avoided deaths can be computed as follows:

$$DeathsAvoided = \frac{\int P_{HTAfterInt}(BP) * RR(BP) dBP - \int P_{HTBeforeInt}(BP) * RR(BP) dBP}{P_{normotensive} + \int P_{HTBeforeInt}(BP) * RR(BP) dBP}$$

Where $P_{normotensive}$ is the proportion of people with systolic blood pressure below 140 mm Hg, $P_{HTAfterInt}(BP)$ is the blood pressure (BP) distribution after the intervention, $P_{HTBeforeInt}(BP)$ is the blood pressure distribution before any intervention, and $RR(BP)$ is the relative risk of dying from or being hospitalized because of a given disease for a given blood pressure. The $RR(BP)$ functions were taken from the meta-analysis of Singh and colleagues.¹²

Data on causes of death and hospitalizations

Mortality data for the UK were taken from the WHO Global Health Estimates (http://www.who.int/healthinfo/global_burden_disease/en/ accessed 22/02/2015), and hospitalizations from Bhatnagar and colleagues¹³ with age distributions from the UK.¹⁴

eText 2. Additional details for data extraction, exposure and outcome definitions

Two reviewers independently excluded articles based on title and abstract or full-text, and abstracted the data. Any discrepancies were resolved in consultation with a third reviewer. From all relevant trials we extracted the first author's name; year of publication; country; calendar year(s) of study conduct; setting of the study; baseline, follow-up, and change in alcohol consumption; nature of the alcohol intervention (eg, counselling, detox, substitution with low alcohol content beverages, administration of alcohol in a hospital setting); age and body mass index (BMI, range, mean or median) at baseline; sex (percentage of men and women); number of participants; baseline, follow-up, and change in SBP and DBP and its standard error or confidence interval by alcohol exposure period; inclusion and exclusion criteria for each trial; and subgroup results defined by hypertension status at baseline and sex.

Because the alcohol content of standard drinks varies around the world (eg, 14 g pure alcohol in the US and 10 g in Australia), we converted reported mean total alcohol intake before and after the intervention in primary trials first into g/day and then standard drinks per day (d/day), assuming 12 g of pure alcohol per drink. Within each trial, different alcohol intake periods with equal alcohol content (eg, 100 ml gin or 272 ml red wine) were combined to yield an overall alcohol reduction effect. Similarly, no alcohol intake periods were combined (eg, de-alcoholized red wine, water).

We restricted our inclusion to trials that reported a change in alcohol consumption with data on alcohol consumption at two periods (high vs low) and a corresponding change in BP measured in mm Hg. In case of duplicate publications of the same trial, we used the most comprehensive data available for each analysis.

We used the reported mean difference (MD, 95% CI) for a corresponding change in BP by alcohol intake, where available. When such an estimate was not available, we calculated the MD (95% CI) in BP between the high alcohol consumption period and the lower alcohol consumption period based on reported means (and standard error or standard deviation) for alcohol consumption and BP for each period adjusted for the correlation between the two periods based on crossover trials with detailed information.^{15,16}

Reference List

1. Laatikainen T, Jula A, Kastarinen M, et al. Verenpaineaset ja hoitotasapaino FINRISKI-tutkimusalueilla 1982-2012 [Blood pressure levels and therapeutic balance in FINRISK study areas in 1982-2012]. *Suomen Laakarilehti* 2013; **68**: 1803-9.
2. Koskinen S, Lundqvist A, Ristiluoma N. Terveys, toimintakysky ja hyvinvointi Suomessa 2011. Tampere: Juvenes Print - Suomen Yliopistopaino Oy, 2012.
3. Banegas JR, Graciani A, de la Cruz-Troca JJ, et al. Achievement of cardiometabolic goals in aware hypertensive patients in Spain: a nationwide population-based study. *Hypertension* 2012; **60**: 898-905.
4. Godet-Thobie H, Vernay M, Noukpoape A, et al. Niveau tensionnel moyen et prévalence de l'hypertension artérielle chez les adultes de 18 à 74 ans, ENNS 2006-2007. *BEH thématique* 2008; **49-50**: 478-83.
5. Neuhauser H, Thamm M, Ellert U. Blutdruck in Deutschland 2008-2011. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). *Bundesgesundheitsblatt* 2013; **56**: 795-801.
6. Llisterri JL, Rodriguez-Roca GC, Escobar C, et al. Treatment and blood pressure control in Spain during 2002-2010. *J Hypertens* 2012; **30**: 2425-31.
7. Catalá-López F, Ridao M, Sanfélix-Gimeno G, Peiró S. Trends of uncontrolled blood pressure in Spain: an updated meta-regression analysis. *J Hypertens* 2013; **31**: 630-1.
8. Joffres M, Falaschetti E, Gillespie C, et al. Hypertension prevalence, awareness, treatment and control in national surveys from England, the USA and Canada, and correlation with stroke and ischaemic heart disease mortality: a cross-sectional study. *BMJ Open* 2013; **3**: e003423.
9. Pater C. The Blood Pressure "Uncertainty Range" - a pragmatic approach to overcome current diagnostic uncertainties (II). *Curr Control Trials Cardiovasc Med* 2005; **6**: 5.
10. Health & Social Care Information Centre. Health Survey for England, 2014 [NS]. 2015. <http://www.hscic.gov.uk/catalogue/PUB19295> (accessed 07/20/2016).
11. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. *Bull World Health Organ* 2004; **82**(11): 858-66.
12. Singh GM, Danaei G, Farzadfar F, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS One* 2013; **8**: e65174.
13. Bhatnagar P, Wickramasinghe K, Williams J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in the UK 2014. *Heart* 2015; **101**: 1182-9.
14. Department of Health. Hospital Episode Statistics 2012/2013. <http://www.hesonline.nhs.uk> (accessed 23/072016).
15. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org (Accessed 07/07/2016).
16. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002; **31**(1): 140-9.

eTable 1. Electronic search of Medline and Embase (through OVID)

Medline(R) (1946-most recent)

| | |
|----|---|
| 1 | Humans/ |
| 2 | randomized controlled trial.pt. |
| 3 | controlled clinical trial.pt. |
| 4 | randomized.ab. |
| 5 | placebo.ab. |
| 6 | randomly.ab. |
| 7 | trial.ab. |
| 8 | Or/2-7 |
| | Alcohol terms |
| 9 | exp Alcohol Drinking/ |
| 10 | exp Alcoholic Intoxication/ |
| 11 | exp binge drinking/ |
| 12 | (alcohol* adj3 (drink* or consum* or intake)).mp. |
| 13 | heavy drinking.mp. |
| 14 | alcoholic beverages/ |
| 15 | or/9-14 |
| | Disease terms |
| 16 | hypertension/ |
| 17 | hypertens\$.tw. |
| 18 | exp blood pressure/ |
| 19 | blood pressure.mp. |
| 20 | (resistant adj2 (hypertension or blood pressure)).mp. |
| 21 | or/16-20 |
| 22 | 1 AND 8 AND 15 AND 21 |

Embase (Embase+Embase Classic)

| | |
|----|---|
| 1 | Human/ |
| 2 | randomized controlled trial/ |
| 3 | crossover procedure/ |
| 4 | double-blind procedure/ |
| 5 | single-blind procedure/ |
| 6 | random\$.tw. |
| 7 | (crossover\$ or cross-over\$).tw. |
| 8 | placebo\$.tw. |
| 9 | (doubl\$ adj blind\$).tw. |
| 10 | allocat\$.tw. |
| 11 | comparison.ti. |
| 12 | trial.ti. |
| 13 | or/2-12 |
| | Alcohol terms |
| 14 | exp Alcohol Drinking/ |
| 15 | exp Alcoholic Intoxication/ |
| 16 | exp binge drinking/ |
| 17 | (alcohol* adj3 (drink* or consum* or intake)).mp. |
| 18 | heavy drinking.mp. |
| 19 | alcoholic beverages/ |
| 20 | or/14-19 |
| | Disease terms |
| 21 | exp hypertension/ |
| 22 | exp blood pressure/ |
| 23 | (blood pressure or bloodpressure).mp. |
| 24 | hypertens\$.tw. |
| 25 | exp resistant hypertension/ |
| 26 | resistant hypertension.mp. |
| 27 | or/21-26 |
| 28 | 1 AND 13 AND 20 AND 27 |

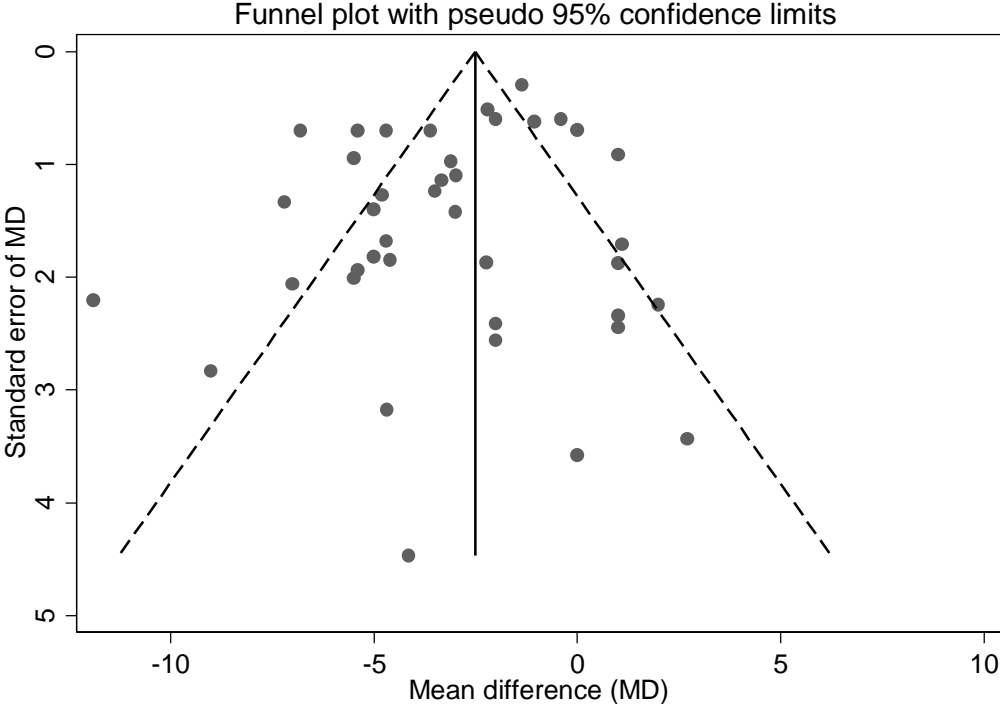
eTable 2. Estimated avoided cardiovascular deaths and hospitalizations for the UK by sex and disease category for adults 35 and older

| Disease category | Avoided hospitalizations | | Avoided deaths | |
|----------------------------|--------------------------|-------------|----------------|------------|
| | Women | Men | Women | Men |
| Rheumatic Heart Disease | 4 | 13 | 0* | 1 |
| Hypertensive Heart Disease | 91 | 241 | 16 | 46 |
| Ischaemic Heart Disease | 360 | 2619 | 46 | 301 |
| Cerebrovascular disease | 272 | 995 | 41 | 124 |
| Other CVD | 480 | 2196 | 22 | 80 |
| All CVD events | 1207 | 6064 | 125 | 552 |
| Total CVD events | 7272 | | 678 | |

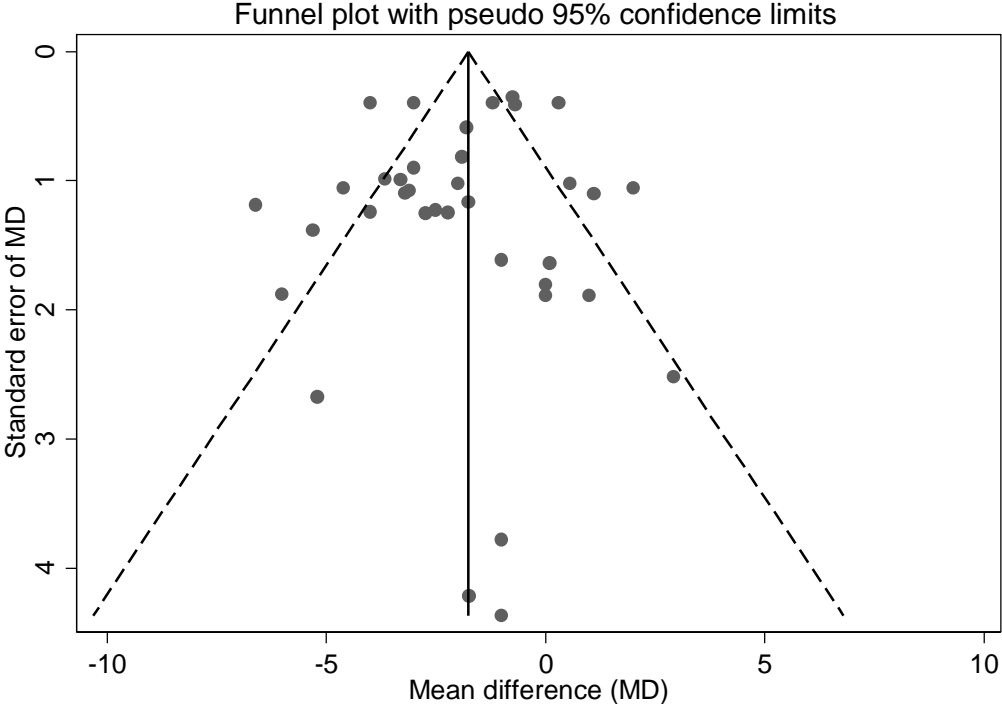
Sums may not add up due to rounding (hospitalizations and deaths were based on attributable fractions (see text) and thus were estimated with decimals.

* 0 means less 0.5 estimated deaths in this category.

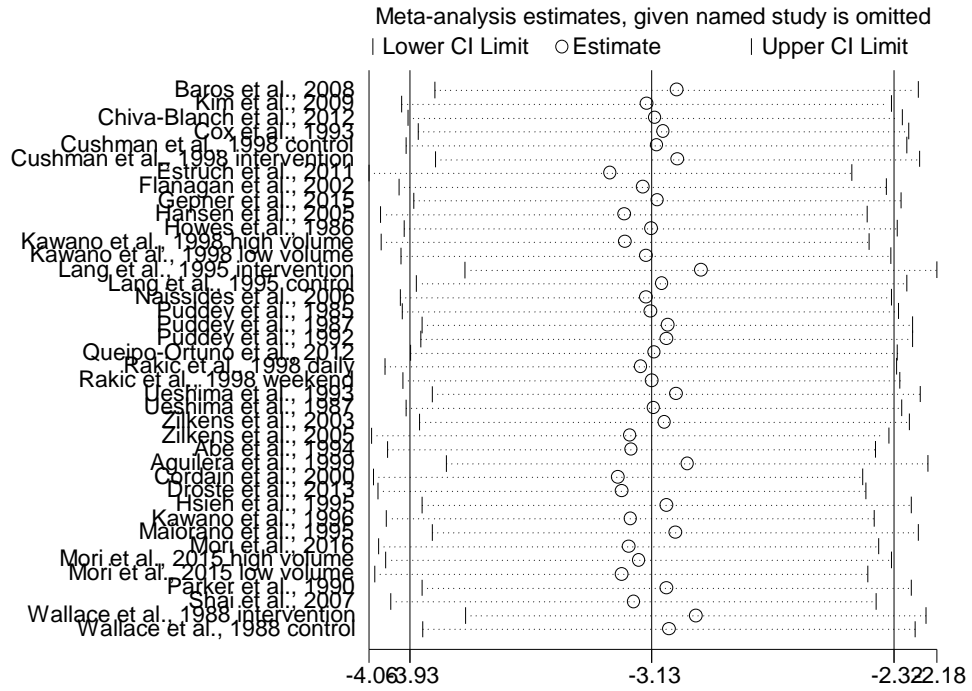
eFigure 1. Funnel plot for all trials, SBP



eFigure 2. Funnel plot for all trials, DBP



eFigure 3. Pooled mean differences after removing each estimate one-by-one, SBP



eTable 3. Cochrane risk of bias analysis

| Reference | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting |
|----------------------------|-----------------------------------|-------------------------------|---|---------------------------------------|--------------------------------|----------------------------|
| Abe et al., 1994 | high | high | unclear | low | low | low |
| Aguilera et al., 1999 | high | high | unclear | low | low | low |
| Baros et al., 2008 | unclear | high | high | unclear | unclear | unclear |
| Chiva-Blanch et al., 2012 | low | unclear | high | unclear | unclear | unclear |
| Cordain et al., 2000 | unclear | high | high | unclear | low | low |
| Cox et al., 1993 | unclear | high | high | unclear | low | low |
| Cushman et al., 1998 | low | high | high | unclear | high | unclear |
| Droste et al., 2013 | low | high | unclear | low | low | low |
| Estruch et al., 2011 | low | high | high | high | high | low |
| Flanagan et al., 2002 | unclear | high | high | unclear | low | low |
| Gepner et al., 2015 | low | unclear | high | unclear | low | low |
| Gepner et al., 2016 | low | unclear | high | low | low | low |
| Hansen et al., 2005 | unclear | high | low | low | low | low |
| Howes et al., 1986 | unclear | high | high | low | low | low |
| Hsieh et al., 1995 | high | unclear | high | high | low | low |
| Kawano et al., 1998 | unclear | unclear | high | low | low | low |
| Kawano et al., 1996 | high | high | high | unclear | low | low |
| Kim et al., 2009 | high | high | high | high | low | low |
| Lang et al., 1995 | unclear | unclear | high | unclear | unclear | unclear |
| Maheswaran et al., 1992 | low | unclear | unclear | unclear | high | high |
| Maiorano et al., 1995 | unclear | high | high | unclear | unclear | unclear |
| Mori et al., 2016 | low | high | high | unclear | high | unclear |
| Mori et al., 2015 | low | unclear | high | low | low | low |
| Naissides et al., 2006 | unclear | high | high | unclear | low | low |
| Parker et al., 1990 | low | unclear | low | unclear | low | low |
| Puddey et al., 1985 | unclear | high | high | unclear | low | low |
| Puddey et al., 1987 | unclear | high | high | unclear | low | low |
| Puddey et al., 1992 | unclear | high | high | unclear | low | low |
| Queipo-Ortuno et al., 2012 | unclear | unclear | unclear | unclear | high | low |
| Rakic et al., 1998 | unclear | unclear | high | unclear | low | low |
| Shai et al., 2007 | unclear | high | high | unclear | low | low |
| Ueshima et al., 1993 | low | unclear | high | low | low | low |
| Ueshima et al., 1987 | low | unclear | high | low | low | low |
| Wallace et al., 1988 | low | unclear | high | low | unclear | unclear |
| Zilkens et al., 2003 | low | high | high | unclear | low | low |
| Zilkens et al., 2005 | low | unclear | high | unclear | unclear | unclear |