Author’s response to reviews

Title: Towards new recommendations to reduce the burden of alcohol-induced hypertension in the European Union

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Dear editors,

Thanks for the reviews and the thoughtful comments. Please find below a point by point description of the resulting changes in the manuscript. We believe to have answered all the points of the reviewers in detail, and as a result, the references increased. Most importantly, we restructured the text by introducing a methods chapter (especially based on the comments of reviewer 1), as well as a chapter discussing economic considerations. Even though our manuscript contains recommendations from the conference in November 2015, we could add new evidence such as the recent systematic review and meta-analyses of RCTs on the impact of alcohol interventions on blood pressure (see below for full reference). In a second round in February/March 2017, all but one of the original signatories (the one could not be reached despite several attempts) of the recommendations (authors) agreed to the current text and reasoning. We hope that the current version is acceptable for publication.
Reviewer reports:

Reviewer #1:

General comment:

This report is an outgrowth of the proceedings of a workshop held a year ago in Barcelona. It is unclear whether the manuscript is primarily a summary of the proceedings of the workshop or an interpretive discussion, as there seem to be elements of both. It would be helpful and of some interest to see the actual program of the workshop. The reader wishes to know what specific presenters offered. At present, several pages of the manuscript are taken by listing of the affiliations of the several dozen participants as well as by potential conflicts of interest or lack of same. However, the actual content of the workshop is unclear.

We reorganized the manuscript completely and introduced a methods section (page 10), where we described the procedure. The actual program of the workshop is now part of the Appendices. However, as laid out in the new methods section, the workshop built on five workshops in different countries (all with a publication which are part of the references: Belgium (1), Finland (2), Germany (3), Spain (4), and the UK (5)), where part of the underlying materials (causality (6-8); meta-analyses on the effect of alcohol interventions on blood pressure (9, 10)) were presented.


Also in need of re-organization is the final section which seems to include sections about recommendations, pilot studies, conclusions, and controlled trials.

We also reorganized the final section (page 22), and restricted ourselves to the recommendations and their implementation. The proposed/started pilot studies and RCT are no longer part of the manuscript. We hope that the reorganized manuscript is clearer.

Specific comments:

A) Abstract:

1. Methods. "Consensus conference based on systematic reviews, meta-analyses, clinical guidelines----. Were any of these new? How were they presented and/or summarized?

This could not be fully explained in the abstract due to word count. However, we have added a new methods section which explains the process in full detail (see page 10, line 5 to page 11, line 3).

2. Results. Starts with "Alcohol use is causally related to high blood pressure." Was this a consensus? It does not appear that new study data are presented. If this is so, Results should start with "The workshop participants concluded that alcohol use ----. "But this immediately raises the issue of the role of alcohol dose and whether there is a threshold effect. I do not think that there is consensus that light drinking raises blood pressure - see below.

A number of points had been raised here.

1) The first sentence has been deleted in the revised version (see page 5, line 3). It was input, and not conclusion of the consensus conference.
2) We did not present new epidemiological data, but a new model of the potential impact of hypertension and alcohol interventions. The whole process leading to the consensus conference has been clarified in the revised paper (see page 10, line 11 to page 11, line 3).

3) Alcohol dose: the reviewer is right, that there is no consensus in the scientific community. We rectified the text accordingly. However, as we are only recommending interventions for hazardous/harmful use of alcohol and for alcohol use disorders (i.e., not for light to moderate consumption), this debate is not relevant for the context of the recommendations.

BTW (completely independent of this text), another group is currently preparing a new meta-analysis based on a NIH grant, which tries to answer the question of impact of light and moderate drinking on BP based on all available evidence to date.

3. Abstract: Line 47: Grammar problem. "------there is lack of implemented these measures -----"

Reformulated (see page 5, line 5).

B) Background

(I) Alcohol and HTN as risk factors for non-communicable disease:

This section discusses WHO goals, which include a 10% reduction in harmful use of alcohol and a 25% reduction in prevalence of HTN. No one could find fault with these modest goals. Salt intake is mentioned as a "Best Buy" for HTN control; it might be best to avoid lingo, or to define such terms. What other measures are advised by the WHO for HTN control?

None, and this is one of the main reasons, why interventions in primary health care should be considered! This reasoning is now laid out in the new section on economic considerations in the revised manuscript (see page 21, line 11 to page 22, line 8).
(II) The evidence for alcohol interventions to reduce blood pressure

This portion of the manuscript is largely a summary of the case for the existence of an alcohol-HTN association and for the belief that reduction of heavy drinking would reduce HTN incidence and/or result in better control of HTN in heavier drinkers with the condition. Again, it is not clear whether this is a consensus of the workshop participants or a statement of the author's ideas.

This process used to reach consensus should be clarified with the revision.

It is stated that the alcohol-HTN linkage is "dose-dependent" (line 55, p 7), but not linear. Actually, it is far from clear that lighter drinking raises blood pressure. Some studies show a threshold effect and some show a J-curve - especially in women, with lighter drinkers at lower risk of HTN than abstainers. There is confounding by under-reporting, which lumps some heavier drinkers into the light-moderate category and blurs a threshold effect. Furthermore, in meta-analyses lumping studies showing a threshold and those without a threshold obliterates demonstration of a threshold.

Sorry, we did not want to touch the controversy of the association between light drinking and blood pressure. This is made clear in the revised version. For the recommendations, it is crucial only, that heavier drinking impacts on blood pressure and hypertension (and we actually modelled thresholds of 60g/day for men and 40g/day for women; see Appendix for details). I am sure the reviewer agrees us and – to our knowledge – all the systematic reviews and meta-analyses, that drinking at and above this threshold impacts negatively on hypertension.

Care needs to be taken to consistently refer to heavy drinking and not just to "alcohol". This report should not be a polemic against any alcohol drinking. A broader context would be desirable. It would be appropriate to mention the fact that light-moderate drinkers have the lowest total mortality, due primarily to lower risk of atherothrombotic vascular disease.

The revised manuscript was checked and any reference to alcohol or drinking impacting on BP was reformulated (e.g. page 11, line 20 to 22).
C) Interventions to reduce alcohol consumption

This section is lucid. Again, I suggest putting the matter in the context of all life-style measures that should be implemented to reduce HTN prevalence and the fact that reduction of heavy drinking has obvious and multiple health benefits, including but hardly limited to reduced HTN prevalence.

Thanks, we did this accordingly (see page 13 and 14).

D) The potential in Europe

The heart of this section is the estimated effect of better HTN screening and addition of brief intervention for hazardous alcohol use or alcohol dependence. The calculations are interesting and the imposing formula in Appendix 1 makes the effort appear mathematically precise. However, it would be appropriate to point out that the structure rests upon assumptions that are estimates at best. But the potential reduction in HTN prevalence from reduction of heavy drinking is surely substantial.

The formula is necessary these days to comply with the GATHER statement (1). All the assumptions are detailed, though, and more care was given to indicate the limitations.


E) Recommendations

There are 4 of these in the results section of the Abstract and in the list of contents, but I find only 3 n this section of the text. This section becomes confusing because of merging of recommendations, pilot studies, conclusions, and controlled trials. Some rewriting is needed here. Perhaps the description of pilot studies and trials would better be relegated to another Appendix. The Conclusions could be briefer and tauter.

Sorry, but due to an editing error one recommendation was erroneously deleted (see page 20, line 15 to 17). As indicated above, we dropped the pilot studies and RCTs from the recommendations (see page 22, line 20 and page 23), and clarified the remaining parts.


Thanks for the references. They were included in the revised manuscript.

Reviewer #2:

This manuscript addresses the potential combined impact of 2 healthcare interventions - screening and treatment for alcohol use disorder and screening and treatment of uncontrolled hypertension - on mortality in the 5 largest European countries. Given the relative prevalence of these 2 disorders and the anticipated results from modelling the outcomes of appropriate therapeutic interventions, the subsequent recommendations of the authors are of major clinical relevance. The approach taken - a consensus conference based on systematic reviews, meta-analysis, clinical guidelines and experimental studies, appears reasonable. I am not able to comment on the appropriateness of the statistical modelling but it has been carefully outlined in the attached appendix and may benefit from independent statistical review.

Thanks! The methodology has been checked by an independent statistical reviewer for the Lancet Public Health contribution (1).


The nature of the relationship between alcohol consumption and hypertension is described as not linear (on P7), with the association stronger at higher drinking levels, but the references quoted (ref 11-14) do not support this contention. In the first reference {alc2047} BP level is related to
the severity of the alcohol withdrawal syndrome in alcoholics admitted for detoxification, not to measured alcohol intake. The second reference, also in a population of chronic alcoholics admitted for detoxification, states that there was a linear relationship between the average daily intake of alcohol in the preceding 3 months and level of BP. It is stated that 46% of patients had a systolic BP > 140mmHg but the relationship to prevalence of hypertension is not described. In the third reference {alc2956} it is stated that there is a dose dependent (linear positive) relationship observed whatever the type of alcohol consumed. The final reference {alc1194} reports "a consistent and positive linear trend" for men but a J-shaped association between increasing alcohol intake and risk of hypertension in women.

The reviewer is right, and we are sorry for the sloppy and indirect citations. As indicated above for reviewer 1, the main thrust of the article was not on light drinking, but on drinking levels, which require interventions, and where the reduction of alcohol would then lower blood pressure levels as well. However, this is no excuse for sloppy citations. This has been corrected in the revised version (see page 11, line 13 to 23).

On page 15, the second recommendation of the consensus conference is to increase screening and brief advice on hazardous and harmful drinking for people with newly detected hypertension from physicians, nurses and other health care professionals in primary health care. The subsequent discussion of evidence grade lists this as firstly as high and then as moderate - does this refer to the 2 levels of drinking - hazardous and harmful? It is unclear as currently laid out. Further none of the references (34, 60-64) specifically refers to alcohol interventions in people with newly detected hypertension.

Mea culpa. For some reason, the third recommendation was erased in the reviewers’ copy. We re-added, and indicated specifically, that there is no evidence yet specifically for people with (newly detected) hypertension in primary health care for Recommendation 3 (see page 20, line 15, to page 21, line 2).

Reviewer #4:

General comments

This is an interesting paper, merging all of consensus, guidelines and modelling approaches to public health policy.
In the Introduction the authors talk about 'best buys' recommended by WHO: "taxation increases, restrictions of availability and a ban on marketing for alcohol use as a risk factor". The paper, though, is 'just' on "screening and brief intervention for hypertension and harmful alcohol use in primary health care". This is a good objective. But the reality is, for the rational policy maker, that the 'best buys' recommended by WHO are (vastly) superior in both health gain and cost effectiveness than anything done in primary care. For example, see this Australian analysis that shows a massive difference in health gains for policies ranging from prevention to high risk to reduce alcohol-related harm. (Cobiac, Vos et al. 2009) and sections within (Vos, Carter et al. 2010) Whilst - of course - analyses of primary care and screening interventions alone are useful, they need to be interpreted against 'what else could be done'. I am sure that the 'what else could be done' in Europe, just as in Australia, would see a much greater (and more cost-effective) impact for what WHO call 'good buys'. Not only does this broaden the scope of what should be done next, but (again, for the rational decision maker) suggests primary care interventions should only be considered once these more fundamental interventions are done first..... generating an intervention pathway or optimal sequence. It is possible to run a counter argument that this current study only considers primary care interventions, or only those interventions that are politically feasible or achievable by the target readership (i.e. guideline audience) - and this is a valid argument to some extent. But for this type of consensus paper, I believe the results and options should be carefully and explicitly contextualized within the full range of options.

The reviewer is correct. We did not want to suggest that alcohol interventions for people with incident hypertension could qualify as best buys. This is made clear already in the introduction (see page 9, line 16 to page 10, line 2).

Furthermore and more importantly, we included a whole new section with economic considerations (see page 21 and 22) which picks up, and hopefully addresses the concerns about why the proposed interventions should be prioritized against, what else could be done in Europe.

p.17. The authors state: "However, in view of the significant evidence for the health harms of heavy drinking and hypertension, combined with the potential gains of the proposed interventions, Europe should not wait for the results of these studies before moving forward with implementation of these recommendations. The precautionary principle, as indicated by the WHO European Region, implies a responsibility to protect the public from exposure to harm where there is a scientifically plausible risk [70, 71]."
This is an unacceptable policy recommendation. Why? Because actual health gain compared to other possible health interventions, and opportunity costs, and cost effectiveness are not considered [see SPECIFIC comments below, and regarding Appendix].

We took off the sentence, and the reference to precautionary principles (see page 24, line 4 to 8). We introduced a whole new section, where cost-economic considerations are discussed (see page 21 and 22).

First, as above (and below w.r.t. Appx) the CRA analysis is good, but does not actually tell us the healthy life years gained (or QALYs gained, or DALYs avoided). To do this requires a simulation model that does allow for morbidity (a person with cirrhosis has a lower quality of life, and high competing mortality and morbidity risk).

We added references to analyses on hospitalizations, QALYs gained, and DALYs avoided (see page 21, line 14 to 16).

Second, there is no mention of cost anywhere in the paper. Diverting primary care time to alcohol screening will have an opportunity cost; something else is not done, or a new cost to the State and taxpayer is imposed. A (rational) policy maker needs to know what the cost effectiveness of this package of interventions might be.

As indicated above, we have given the necessary information in a new paragraph (see page 21 and 22). A recent analyses showed that national implementation of screening and brief intervention is not only cost effective in 24 of 28 EU countries, but also cost saving in 50% of these countries (1).


Thus I suggest the authors' recommendations are over-reach, and should be framed in terms of:
These interventions are likely cost effective [I suspect they will be], but need to be assessed by way of:

a. Simulation models now given what we know (see Australian study for example)

b. Cost-effectiveness models attached to the proposed RCTs.

We hope that with the new sections and the work of Angus, this is clarified (see page 21, line 19 to page 22, line 2). If the intervention has been found to be cost-saving in 50% of the EU countries in models, this would underline that the current recommendations are not overreach.

I understand why the authors invoke the precautionary principle, but I think it is a slight misuse. A better framing, perhaps, might be that they recommend these policies are implemented, but carefully evaluated as implemented (especially for cost effectiveness) so that they can be fine-tuned or abandoned as necessary. That is, policy-generating-evidence is probably acceptable here - but it must be framed that way.

We changed the revised text accordingly, and suggested a strong economic part of the evaluation (see page 22, line 11 to 19).

SPECIFIC COMMENTS:

p.5, lines 12-22: “There are a number of European studies planned or being conducted to examine feasibility and/or effectiveness of these recommendations. However, given large deficits in dealing with both conditions and the existing evidence base for the recommendations, efforts to foster routine screenings and other recommendations should start immediately.” The last sentence of the abstract seems premature, unless the interventions are feasible, effective and cost effective; the Abstract does not make this clear enough to the reader to have the second to last and last sentence juxtaposed as it is now.
We dropped the announcement of studies, and introduced the rationale (see Abstract, page 4).

p.8. It might be useful to give PAR% or population impact fractions from the GBD on the theoretically possible reduction DALYs if alcohol shifted to TMREL in European countries - so long as DALYs expressed in some meaningful unit (e.g. per capita, or as % of all DALYs lost in Europe, etc). It would also provide context for the authors’ CRA.

The recommendations are about alcohol interventions in a very specific context, i.e. for newly detected hypertensives. To give PAFs or the like for alcohol as a whole would be misleading in our view in this context.

p.8 line 57 to top of p.9. But what is prevalence of AUD in non-hypertensive? (Which relates to above suggestion of PAR%.)

The information has now been added to the manuscript (see page 13, line 18 to 21).

p.9 line 16. What was comparator group for OR? Presumably just a dichotomous split AUD vs non-AUD?

Yes

p. 9, line 46. "Over five weeks of measurement during 2013-2014, out of about 900,000 adult consultations (about 1200 consultations with 746 providers), only 1.4% of adult consultations resulted in patients being screened and given advice for their heavy drinking [41, 42]." I am not sure I agree. Given the huge diversity of presentations to primary care, that each person has multiple consultations with a GP (or other primary care provider) over time (i.e. more than this cross-sectional slice), 1.4% may not be bad going.

We gave more information about the screening part based on the publication, and believe, that is good reason to state, that screening and brief interventions was too low (page 14, line 10 to 13).
Table 1 footnotes. Was it greater than 140mmHg systolic to be HT, or both 140 systolic and 90 diastolic?

As in the footnote, the proportions are for 140/90 mmHg (see page 16, line 4). The modelling later was restricted to systolic BP (page 16, Table 2).

p.10 to p.11. The table captions say 40-64 year olds, but I think the reader needs reminding in the text too.

Added (see page 15, line 5; page 16, line 10, page 17, line 9).

Table 3. [See comments below on method in Appx.] CRA methods will overestimate the deaths averted. This is not too severe for CVD (as timelags short), but is more of a problem for liver cirrhosis. Yes, one sees pretty rapid changes in liver cirrhosis deaths with changes in alcohol consumption - but the full benefit (i.e. that implied by the RR which reflects longer term differences in alcohol consumption) will not be realized for some years, given cirrhosis is a chronic condition. This needs acknowledging as a limitation.

1) Our estimate may not overestimate too much, as we did not include cancer, which has the largest lag (see page 18, line 10 to 11).

2) As for liver cirrhosis, while the disease may take a long time to develop, deaths react very quickly to reduction of drinking (anecdotally, see the invasion of Paris by the Germans with the confiscation of wine and the subsequent drop of liver cirrhosis mortality; the drop of liver cirrhosis mortality at the begin of prohibition or the drop when Gorbachev reduced overall alcohol consumption in the Soviet Union).

3) We did introduce the concept of CRA (page 17, line 14) and some considerations concerning lag times (see page 18, line 11 to 12) to the revised article.
APPENDIX

p.20. Why a belly curve? It reads as though it is a log-normal distribution. A distribution very common in biology and public health. That said, the belly curve seems to work. I do, and I assume the reader too, will be curious as to why a log normal distribution was not used though.

The curve used is the easiest to use with the fewest parameters and modelled the data well. A recent statistical review of the curve during a Lancet Public Health submission (1) showed no problems.

The Method is a comparative risk assessment (CRA) method; i.e. estimate change in BP distribution for a given intervention, integrate before and after with RR function, and thereby estimate proportion of deaths avoided. An extension of PAR% methods. This is appropriate, but also has limitations as applied here that need acknowledging:

a. As with many models of this 'cross-sectional' nature, deaths prevented are estimated as though the change in risk factor had the immediate impact suggested in meta-analyses. For BP and stroke/CHD, this is probably not too far out (time lags are not long - unlike cancer aetiogenesis). Nevertheless, time-lags are not included.

As indicated above, we have now included the points on lag time (see page 18, line 11 to 12). As we purposefully excluded alcohol’s impact on cancer because of long lag times, we should not be too far off.

b. A grave limitation of the CRA method to deaths averted is the failure to capture the years of (healthy) life saved. It sounds useful to say that X deaths averted, but at what age? How much life gained? Etc. For a publication in high impact journals, I think some estimate of (healthy) life years gained is required.

All deaths are premature, as we only modelled people ages 40 to 65 (see page 15, line 5; page 16, line 10, page 17, line 9).

c. The cross-sectional CRA approach does not allow for attrition of intervention effect. Thus, whilst (say) 50% of target population are assumed covered (good), there is no allowance for attrition of intervention effect (e.g. people ceasing medication, relapsing to high alcohol consumption, etc). This will - in the real world - result in much less health gain than suggested in the analysis. That is the results in Table 3 are optimistic, although the authors do frame it in
terms of "within 12 months" without falsely implying this amount each year for many years - which is a sensible framing.

We stressed the effect to one year, and we introduced the concept of attrition (see page 17, line 13 to 16).
