PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What is the optimal level of population alcohol consumption for chronic disease prevention in England? Modelling the impact of changes in average consumption levels
AUTHORS	Melanie Nichols, Peter Scarborough, Steven Allender and Mike Rayner

VERSION 1 - REVIEW

REVIEWER	Saverio Stranges University of Warwick Medical School
REVIEW RETURNED	08/02/2012

GENERAL COMMENTS	**Manuscript ID: bmjopen-2012-000957** **What is the optimal level of population alcohol consumption for chronic disease** **prevention in England? Modelling the impact of changes in consumption patterns** Overall, this manuscript could potentially provide an important contribution to the longstanding issue of harms and benefits of alcohol consumption in terms of burden and mortality from major chronic disease. Authors attempted to estimate the impact of achieving alternative population alcohol consumption patterns on chronic disease mortality in England. While it is well established that excess alcohol intake is associated with a wide range of harmful effects on chronic disease morbidity and mortality, there is still uncertainty about the threshold of alcohol intake at which harms may outweigh potential benefits of moderate amounts of alcohol on cardio-metabolic health, with a reduced risk of CVD and type 2 diabetes, as supported by a large body of observational evidence. The present study suggests that actually the dosage of alcohol associated with the lowest risk of chronic disease mortality may be much lower than previously thought. The concluding remarks of the authors are that "…current government recommendations for alcohol consumption are well above the level likely to minimise chronic disease. Public health targets should aim for a reduction in population alcohol consumption to half a unit per day, in order to achieve the optimum level of reduced chronic disease mortality". The authors should perhaps attenuate the assertive, definitive tone of their conclusions, because their findings are based on a series of assumptions and statistical modelling, which may not entirely reflect the "truth". There are a few specific concerns with the present manuscript, which are outlined below: 1) In general, throughout the manuscript, I would suggest to use a less definitive tone because this is only one single study in one specific setting. Findings might be different in settings where

	drinking patterns are substantially different from the UK or Northern Europe, where the prevalence of binge drinking is certainly higher than, for example, in Southern Western Europe. 2) The title of the manuscript is misleading, because the authors were not able to examine specific drinking patterns, such as drinking intensity or frequency, beverage preference or drinking in relation to mealtimes, due to the intrinsic limitations of their data. 3) I wonder if the authors could use, alongside absolute numbers of deaths, more comprehensible measures to a wider readership, for example percentage reductions in mortality outcomes. 4) There are a large number of tables and supplementary figures, which are difficult to interpret. Please do explain your results using a less technical language. 5) The authors mentioned a previous meta-analysis by Di Castelnuovo et al in 2006, which would report similar results. However, to my understanding, in that paper the authors found a relatively higher threshold (1-2 drinks per day for women and 2-4 drinks per day for men) associated with reduced total mortality, as compared to half a unit per day reported in the present study. 6) Finally, the authors should explain to the readers what half a unit per day means in terms of specific alcohol beverages (e.g. half glass wine, one pint lager, etc…).

REVIEWER	Jennie Connor Professor and Head of Department Preventive and Social Medicine Dunedin School of Medicine New Zealand I have no conflicts of interest relevant to this manuscript.
REVIEW RETURNED	18/02/2012

THE STUDY	Limitations in exposure measurement, outcome measures and lack of accounting for pattern of drinking are given in the review. The literature on the methodological shortcomings of studies of CVD and alcohol is not discussed/referenced. Likewise guideline development or drinking guidelines. There are more limitations than are noted.
RESULTS & CONCLUSIONS	A simplistic and narrow approach has been taken to answering the research question they chose. The specific question and they way it has been addressed doesn't support the recommendations.
GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. I had some difficulty working out the overall purpose of the study. The relationships between the “adequacy” or otherwise of the current guidelines, the estimation of a an optimal counterfactual drinking distribution for a selection of conditions and healthy public guidance on alcohol was not clear to me. Firstly, considering the modeling exercise devoid of its context, which is what the authors largely do, I would make several major points: 1. The evidence about benefits of alcohol for CVD and related conditions is contentious and there is an expanding research

	literature about this that is not referred to. The implications of the meta-analyses of cohort studies of CVD being biased by the shortcomings common to all of the studies are critical to this kind of exercise. The possibility that the benefits are substantially inflated by uncontrolled confounding and that the doses of alcohol required for effects are underestimated has a profound influence on the conclusions, and I would argue (later) that the benefits should be omitted. Not acknowledging the sensitivity of the model to this major source of uncertainty is not scientifically rigorous. 2. The authors have restricted their scope to chronic diseases as if this was a separate question from other conditions (for which there would be different guidelines perhaps?) While I don't think this is helpful, it does not get the investigators out of having to consider pattern of drinking. There is no question that the cohort studies that underpin the "benefits" of drinking alcohol do not measure pattern adequately and thus, while they may capture average risk in the particular population (if underreporting of consumption were to have been adjusted for) they can not be considered predictive of the effects of drinking in any particular pattern. So if 5g/day really was a credible estimate there is no way of knowing from these studies whether it can be all consumed on one day a month or needs to be a daily dose. In summary, this is the wrong exposure measure and has not been well measured, even though there are lots of big studies and they have been combined in numerous meta-analyses. There have been considerable advances in modelling the pattern sensitive nature of CVD benefits that are not mentioned here. (Global Burden of Disease 2005 CRA Alcohol group) Secondly, this study can not be considered out of it's context. The purpose is clearly something to do with giving good advice on healthy drinking patterns. I have a few more comments on this. 3. The study inherently treats the positive and negative effects of alcohol consumption as of equal value and takes the position that they can be traded off against each other. So this means that the death of a sixty-year-old woman from liver cancer arising from alcoholic cirrhosis has the same value as delaying a death from CVD in another person at another age. There are several flaws in this argument. One obvious technical one is measuring the number of deaths (which have been called " mortalities") vs years of life lost or DALYs. So there is an inherent problem with the outcome measure that is not discussed. It becomes an even bigger issue when the study is placed back in the real world where much alcohol damage occurs in the younger population. However, the most important flaw is that the liver cancer death is preventable in the counterfactual where she didn't drink at all, and the CVD deaths are also preventable without alcohol. In the countries where all of these data come from, we have comprehensive evidence-based guidelines for reduction of cardiovascular risk. They employ safe medications that are known to be effective, and are not carcinogenic, intoxicating, addictive, or toxic. They are very seldom taken in overdose and they are readily available. The implication of this study that alcohol is an appropriate intervention (at 5g/day) to be promoted for CVD prevention either has not been considered or is naïve.

	4. In formulating a recommendation for a guideline there are some unresolved issues: This study does not account for anything about CVD morbidity, mortality or prevention except for the dubious benefits of alcohol. I find this simplistic approach disingenuous and misleading. The primary analysis could be one where chronic harm alone is modelled against consumption. The shape of this function could inform a choice about what level of harm we might agree was acceptable given the social benefits of alcohol. The authors do not discuss what level of drinking guideline might be required to shift the population distribution to consumption to a median of 5g/day. This would not necessarily be a recommendation that everyone drink at that level. There is no indication that the authors are familiar with the wider discussion about drinking guidelines. Plenty of evidence currently supports the author's conclusion that the existing drinking guidelines are not evidence-based and are too high. However, I think there is a possibility that they are propagating an even greater harm to public health in this paper. That is, that the promotion of the pro-health impacts of alcohol consumption, and particularly of the daily consumption of alcohol. The promotion of alcohol consumption for health benefits, no matter how it is couched, affects the perception of the acceptability of drinking at all ages in all amounts. Advice from health professionals is an important contributor to that perception that is milked by commercial interests, and the overall effect on population health need to be considered. Guidelines and expert advice are not context-free and need to be based on much better evidence than this. To counter the argument of the Australian Cancer Council that people would be best to avoid alcohol consumption altogether, the authors claim "Only by systematically combining the effects of alcohol on all alcohol-related conditions can appropriate public health messages be developed." They haven't done this and the paper appears to be supporting pro-alcohol messages in an unbalanced way.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Saverio Stranges, University of Warwick Medical School

Specific concerns:

1) The authors should perhaps attenuate the assertive, definitive tone of their conclusions, because their findings are based on a series of assumptions and statistical modelling, which may not entirely reflect the "truth". Findings might be different in settings where drinking patterns are substantially different from the UK or Northern Europe, where the prevalence of binge drinking is certainly higher than, for example, in Southern Western Europe.

Thank you for this advice on the tone of the paper. We have altered the wording throughout as suggested. See for example:
Line 405, page 12 – 'Based on this model…' added
Line 400, page 12 – inserted 'potential': 'demonstrates the potential impact of population alcohol consumption…'
Line 539, page 16 (conclusions) - 'our modelling suggests that…'

Line 454, page 13 – replaced ‘results’ with ‘predicted impacts’
In addition, we have emphasised further in the discussion that results may vary substantially in other contexts where the current levels of alcohol consumption and underlying levels of disease and other risk factors are different (lines 500-504, page 15).

2) The title of the manuscript is misleading, because the authors were not able to examine specific drinking patterns, such as drinking intensity or frequency, beverage preference or drinking in relation to mealtimes, due to the intrinsic limitations of their data.

We agree that the use of ‘patterns’ was not well advised, and have altered the title to better reflect the aspects of alcohol consumption that we did examine in the manuscript. The title now reads:
"What is the optimal level of population alcohol consumption for chronic disease prevention in England? Modelling the impact of changes in average consumption levels"

3) I wonder if the authors could use, alongside absolute numbers of deaths, more comprehensible measures to a wider readership, for example percentage reductions in mortality outcomes.

We have now indicated in the text of the results the percentages of reductions in annual mortality for the key results overall and by condition. See lines 302-307, page 11 and 369-373, page 12.

4) There are a large number of tables and supplementary figures, which are difficult to interpret.

The supplementary information has been reduced to 4 items (from 7) and additional information has been added to the labels to clarify their purpose and interpretation.

5) The authors mentioned a previous meta-analysis by Di Castelnuovo et al in 2006, which would report similar results. However, to my understanding, in that paper the authors found a relatively higher threshold (1-2 drinks per day for women and 2-4 drinks per day for men) associated with reduced total mortality, as compared to half a unit per day reported in the present study.

While it is correct that Di Castelnuovo and colleagues found reduced risk of total mortality (compared to non-drinkers) over a range of alcohol consumption levels, continuing up to a higher threshold, the lowest mortality found in their meta-regression analysis was at 6g/day (RR 0.81 see p2440). In this sense the results are very much consistent with our findings. Although not directly comparable, our results also predict reduced chronic disease mortality in the English population up to higher levels of consumption (in fact, at any median level of consumption that is below the model’s baseline median level of 13g/day).

6) Finally, the authors should explain to the readers what half a unit per day means in terms of specific alcohol beverages (e.g. half glass wine, one pint lager, etc…).

Thank you for this very useful suggestion. The following descriptions have been incorporated into the introduction and discussion respectively to clarify this.
“one pint of standard beer contains approximately 2 to 3 units, and a 175ml glass of wine approximately 2 units” See lines 168-70, page 6
“This level of consumption [5g/day] would equate to as little as one quarter of a glass of wine, or one-fifth of a pint of beer per day on average.” See lines 384-85, page 12

Reviewer 2: Jennie Connor, Dunedin School of Medicine

Major points:

1) The evidence about benefits of alcohol for CVD and related conditions is contentious and there is an expanding research literature about this that is not referred to. The implications of the meta-analyses of cohort studies of CVD being biased by the shortcomings common to all of the studies are critical to this kind of exercise. The possibility that the benefits are substantially inflated by uncontrolled confounding and that the doses of alcohol required for effects are underestimated has a profound influence on the conclusions, and I would argue (later) that the benefits should be omitted.

We acknowledge that the results are heavily dependent on the quality of the evidence available to parameterise the model, as in any modelling exercise. To be clearer about these issues, we have expanded our discussion of the limitations of the evidence (see lines 435 to 444, and article summary, strengths and limitations dot-points). These limitations can never be entirely removed from a modelling study, however we feel that they have been clearly represented in the paper and the meta-analyses used and the adjustments made are included in table S1. The results produced by the model can only be interpreted in the context of accepting the current best available level of epidemiological evidence for the relevant relative risk - which applies equally to all of the conditions considered in the model. For this reason, we took an a priori decision to only include conditions in the model where an appropriate meta-analysis was available, although we acknowledge there may still be bias in the results of meta-analyses if all of the contributing studies have common or systematic biases. Further discussion of the controversies within the literature around the protective effect of alcohol has been added, see lines 458-461, page 14.

2) The authors have restricted their scope to chronic diseases … it does not get the investigators out of having to consider pattern of drinking. […] So if 5g/day really was a credible estimate there is no way of knowing from these studies whether it can be all consumed on one day a month or needs to be a daily dose. In summary, this is the wrong exposure measure and has not been well measured, even though there are lots of big studies and they have been combined in numerous meta-analyses.

Patterns of drinking are of course a very important consideration, however average consumption levels are also widely used in the literature, and has been shown to have an important relationship to disease (e.g. Rehm 2006, Addiction 101(8)). As discussed in lines 442 to 452 (page 14), the pattern of drinking has not been explored and needs to be considered further in future research to ensure reduced harms. This is also highlighted in the key messages under strengths and limitations.

3) The study inherently treats the positive and negative effects of alcohol consumption as of equal value and takes the position that they can be traded off against each other. So this means that the death of a sixty-year-old woman from liver cancer arising from alcoholic cirrhosis has the same value as delaying a death from CVD in another person at another age. One obvious technical one [flaw] is measuring the number of deaths vs years of life lost or DALYs. So there is an inherent problem with the outcome measure that is not discussed.

Although our model is not set up to estimate effects on DALYs or YLL, a strength of the model is that it employs age- and sex-specific mortality and alcohol consumption data, and the estimates of deaths delayed or averted produced are also age- and sex-specific. These results had been summed to provide overall estimates of the net effect for the population in our results, however we have now included additional results emphasising the age-specific modelled estimates of changes in mortality with changes in alcohol consumption. See lines 305-307 and lines 312-315, page 11. We have also noted this limitation more clearly in the discussion, see lines 416-419, page 13.

4) The implication of this study that alcohol is an appropriate intervention (at 5g/day) to be promoted

for CVD prevention either has not been considered or is naïve.

This is certainly not our interpretation of the evidence, nor our intended recommendation. Our discussion very clearly states that adopting alcohol drinking among those who currently do not consume it is an inappropriate approach or recommendation (see lines 408-416). In order to further clarify this (as well as addressing several other concerns raised in these reviews), we have significantly edited and restructured our results presentation, and removed some of the results that refer to modelled changes in proportions of non-drinkers. Our aim with these revisions is to further emphasise the results related to average consumption levels, since these are the most relevant to our recommendations as a result of the modelling exercise. The idea that alcohol is effective in preventing CVD is a common message that is in wide circulation in the community and media, and appears to be used quite extensively by both industry and drinkers to justify alcohol consumption, while selectively ignoring the concurrent health risks. Our modelling, rather than supporting this view of alcohol as a preventive strategy, shows that the levels of alcohol that would actually be likely to be associated with reduced risk of chronic disease, when multiple conditions are considered simultaneously, are much lower than is generally accepted, or recommended by government. An additional key message has been added to the start of our paper to emphasise this interpretation of the results.

5) In formulating a recommendation for a guideline there are some unresolved issues. This study does not account for anything about CVD morbidity, mortality or prevention except for the dubious benefits of alcohol.

This paper aims specifically to explore the potential effect of changing levels of average alcohol consumption on chronic disease mortality in the English population. Examination of the simultaneous roles of other factors related to CVD is beyond the scope of this paper, but is recommended for further research (see lines 508-510, page 16). The contribution that this paper seeks to make is to balance the apparently protective effect of modest alcohol consumption on CVD, with the many other increased risks of chronic diseases associated with alcohol consumption. There is clearly much more than this to be considered when an overall population guideline is formulated, and this is emphasised in the discussion and conclusions (see 403-416, 424-434, 473-474, 497-501).

6) The authors do not discuss what level of drinking guideline might be required to shift the population distribution to consumption to a median of 5g/day

Additional discussion has been added (see lines 421 – 425, page 13) around the possible contribution of this modelling, and the importance of other factors, in setting guidelines. It is beyond the scope of our work to estimate the effectiveness of alcohol guidelines in changing alcohol consumption patterns.

7) Plenty of evidence currently supports the author's conclusion that the existing drinking guidelines are not evidence-based and are too high. However, I think there is a possibility that they are propagating an even greater harm to public health in this paper. That is, that the promotion of the pro-health impacts of alcohol consumption, and particularly of the daily consumption of alcohol … the paper appears to be supporting pro-alcohol messages in an unbalanced way.

We thank the reviewer for this feedback. Although it was of course never our intention to suggest 'pro-alcohol messages', on reviewing the presentation of our results it is apparent that we had not been careful enough to avoid this impression. We have therefore made significant changes to the results presented, in addition to revisions to the abstract, discussion and conclusions, in order to ensure that our central message – that current recommended levels of alcohol consumption are not consistent with the lowest risk of chronic disease (as highlighted in the 'article summary' key messages section) – is not obscured or left open to misinterpretation.

As discussed above, we have re-focussed the paper overall to emphasise more clearly the results for varying levels of average alcohol intake, in the scenario for which the percentage of non-drinkers in the population is held steady. In particular, the primary results table in the main document has been changed to present these results rather than the 'theoretical optimum' results in which there were no non-drinkers in the population. This now emphasises the results which are most relevant to appropriate public recommendations, rather than those which have produced the greatest modelled reductions in mortality. Note that figure 1 and 2 have been renumbered (numbers swapped) as a result of this change in the results.
In addition, as we acknowledge that any reduction in the proportion of non-drinkers is of little practical relevance to public health recommendations, and current non-drinkers should not be encouraged to start drinking regardless of the possible chronic disease implications modelled here (see lines 408-419, page 13), we have removed the third counterfactual scenario from the paper, which set the proportion of non-drinkers at 0% and varied the median consumption level.

VERSION 2 – REVIEW

REVIEWER	Jennie Connor Head of Preventive and Social Medicine Dunedin School of Medicine University of Otago NZ No competing interests
REVIEW RETURNED	08/04/2012

RESULTS & CONCLUSIONS	The authors have advocated for their results to be used as a target for daily drinkng limits, even though they haven't considered anything other than chronic disease mortality in their modelling. That is, they haven't considered injuries, and they haven't considered morbidity. I still consider that the authors have inadequately expressed the weaknesses of the evidence about CVD benefit from alcohol. They have made an assumption that the metaanalyses reflect the truth, but they haven't discussed the implications of this assumption. They are trading off deaths from other diseases, for example cancer, against putative CVD benefits that could be gained through following appropriate CVD risk reduction guidelines. Putative benefits for CVD are promoted as being pattern-dependent but neither the CVD meta-analyses referred to nor the model described in this paper take drinking pattern into account.

REVIEWER	Saverio Stranges, MD, PhD Associate Professor of Cardiovascular Epidemiology Statistics & Epidemiology Division of Health Sciences University of Warwick Medical School Medical School Building Gibbet Hill Campus Coventry
REVIEW RETURNED	16/04/2012
GENERAL COMMENTS	The authors have satisfactorily addressed previous concerns, which were raised as part of the review process.