Author’s response to reviews

Title: The relationship between mild alcohol consumption and mortality in Koreans: A systematic review and meta-analysis

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Author’s response to reviews:

Major Compulsory Revisions

1. Please provide a summary table of essential information of all the studies included in this review and meta-analysis, especially the measures of alcohol consumption and categorisation/definition of ‘mild’ drinking in these studies.

# We did not add table 1, which summarize each study, by mistake. We add the table in page 18. This table include measures of alcohol consumption, risk of each category, and criterion of mild drinking.

2. It’s not clear how comparable the ‘mild’/‘moderate’ drinking in this review is with other widely used gender-specific categorisations of light-to-moderate drinking in literature. Please add it in the paper. Also, is ‘mild’ drinking equivalent of ‘moderate’ drinking in this paper? Please be consistent.

# Although there is a moderate drinking criteria according to ‘Dietary Guidelines for Americans’, the range of alcohol amount showing protective effect was different between studies. We compared the risk of non-drinkers and the group consuming alcohol least among alcohol drinkers, based on each study. Several included studies (Jeong 2012, Lee 2002) divided drinkers as light/ moderate/ heavy drinker, and we used the risk of light drinker as experiment group in this review. So, we described as ‘mild drinker’ to avoid confusing, and to focus that they drink alcohol least. I added some explanation about this in page 4-5 as follows:

Also, for consistency, we changed the expression into ‘mild’ in text and figures. Thank you for your advice.

: Although there is a consensus on moderate drinking as up to one per day for women and up to two drinks per day for men,[15] the range of alcohol amount showing protective effect in previous meta-analysis was various. [6-8] So, we compared the risk of non-drinkers and mild drinkers consuming alcohol least based on each study’s criterion.

3. Does the ‘mild’ drinking in this review/meta-analysis include other categories of
alcohol consumption? For example, a) did the three studies used drinking status contain a category of ‘mild’ drinking? If study subjects were only divided into non-drinkers and current drinkers, it would not be appropriate to include these studies in the meta-analysis as they failed to separate ‘mild’ drinkers from heavier drinkers; and b) in studies only measured drinking frequency, the drinking volume is unknown and the ‘mild’ drinking is not applicable. It is possible that those ‘mild’ drinkers based on drinking frequency may be heavy drinkers who consume alcohol infrequently.

We conducted meta-analysis including not only studies using amount, but also studies using status/frequency because of small number of studies. However, we conducted meta-analysis separately, and added the result of those as sub-analysis. (page 7)

: The result of subgroup analysis excluding studies using drinking status [23, 24] (OR: 0.9, 95% CI: 0.78, 1.04), or status/frequency [1, 23, 24, 26] (OR: 0.85, 95% CI: 0.72, 1.01) to investigate only the effect of mild drinking remained non-significant.

4. Please discuss how this study is influenced by: a) use of non-drinkers as reference group; and b) inclusion of ‘sick quitters’ (former drinkers who quit drinking because of health reasons) in the category of non-drinkers.

We added the paragraph about this topic in discussion section. (page 10)

: Most of included studies used non-drinker as reference group, however, it is unclear whether those studies include former drinker to non-drinker. Because some former drinker quit drinking because of health reasons, analyzing those as non-drinker could cause biased results. Not only drinker misclassification including former drinker with non-drinker, also including occasional drinkers with non-drinker or low-level drinker could bias risk estimates [42]. Classification of drinker is important in assessing the risk of alcohol consumption.

5. Please give some possible explanations of population heterogeneity found in the meta-analysis.

In discussion section, we added the explanations of population heterogeneity as follows: (page 10)

: The age of included subject in each study was various. Several studies included subjects based on their living area [1, 24, 25, 28, 36, 37], the others included subjects on health examination [26, 27]. For those reason might contribute to population heterogeneity in this meta-analysis.

6. Please discuss in more detail regarding: a) possible gender difference in drinking behaviour or drinking pattern in Korea, and how it is related to mortality; and b) residual confounding (e.g. differences between non-drinkers and moderate drinkers) and the potential of Mendelian Randomisation to explore alcohol consumption and mortality.

We added explanation regarding this topic in discussion, 6th paragraph. (page
10) In this review, several studies used different criterion between men and women [26, 36], and other studies applied same criterion and analyzed both sex together. In previous meta-analysis investigating alcohol and total mortality, 2-4 drinks per day for men and 1-2 drinks per day for women are inversely associated with total mortality [6]. Women may be more vulnerable to alcohol-related risk, men and women show different drinking pattern [39]. Participants' factors such as sex, should be considered when assessing the impact of alcohol.

7. In background, 2nd paragraph, it was stated that ‘the effect of alcohol might be different by health status’. Please discuss how health status may affect the results in this paper.

# We added two sentences supporting the difference of alcohol effect by health status. If there should be more explanation, please let us know. (page 3)

: In addition, the effect of alcohol might be different by health status. Previous study reported that moderate alcohol use may be beneficial for older adults in poor health, but not for adults in good health [10]. Also, the risk of alcohol consumption on cardiovascular disease was different between men with hypertension and without hypertension.[11]

Minor Essential Revisions
1. Results, 2nd paragraph, ‘drinking criterion’=measure of alcohol consumption?
# We changed the expression as recommended. (page 6)

2. Results, section of cancer-related mortality, please add references to the four studies examined all cancer morality, as well as those investigated specific types of cancer.
# We added the references in text. Also, it is described in table 1. (page 7)

3. Discussion, 2nd paragraph, it is confusing that 2-4 drinks per day for men=6-42 g/day? 2 drinks=6 g of alcohol?
# We modified the sentence to be clear. (page 10)

4. Discussion, 3rd paragraph, please add the reference to the total alcohol per capita in Korea.
# We added the reference in the end of the sentence. (page 9)

Thank you for all valuable comments.

Reviewer’s report
Title:The relationship between mild alcohol consumption and mortality in Koreans: A systematic review and meta-analysis
Version:2Date:21 March 2015
Reviewer: Claire Mawditt
Reviewer's report:

Major Compulsory Revisions
None

Minor Essential Revisions
1. There is some inconsistency in wording in relation to the level of alcohol consumption under investigation. The title refers to mild alcohol consumption [line 1], at times the article refers to both mild and moderate consumption [line 55 and figure 2]. Language should remain consistent.
   # We modified the expression into ‘mild’ in text and figures 2-4.

2. Line 59 - remove “also” from the sentence “Rehm et al. also reported a significant influence of drinking on mortality with a J-shaped”.
   # We modified the sentence as recommended. (page 3)

3. Line 88 refers to the extraction of risk ratios from each study. However, the tables in figure 2 refer to odds ratios. This inconsistency needs to be clarified.
   # The individual studies used various risk estimate including relative risk, hazard risk, and odds ratio. So, we did not describe the type of risk in text as follows. we transformed risk into odds ratio in meta-analysis. (page 4)

4. Line 131 refers to figure 2. It should be clarified which outcome, each table in figure 2, refers to. Replace “moderate” drinking with “mild” drinking for consistency. Should the table say odds ratios or risk ratios? (Line 88 refers to risk ratios).
   # We changed the term into ‘mild drinking’ in figures. The risk of mild drinking in included studies transformed into odds ratio in meta-analysis. (figure 2,3,4)

5. The sentence on line 159-160 does not make sense and needs to be re-worded. “Cause of small number of studies in each outcome, statistical test did not conducted.”
   # We modified the sentence as follows. (page 8)

   # We modified it as recommended. Thank you for pointing out our mistake. (page 9)

7. Line 186 - replace the word “took”. This wording is incorrect. Possible replacement could be “accounted for”.
8. Line 186 - Remove the word “consequently”, this is not appropriate for the sentence because the factors mentioned in line 187 (age, sex, lifestyle) have not been mentioned previously.

# We modified the sentence as recommended. (page 9)

9. Line 198 - A reference should be provided for the statement “high-dose ethanol increase mortality”.

# We added the reference. (page 11)

10. Line 200 - states “the mechanism of alcohol on health”, this should be changed to the “biological mechanism” or “physiological mechanism”.

# We changed the expression as recommended. (page 11)

Discretionary Revisions

11. Line 113 refers to table 1. I have not been able to locate this table and review its contents.

# We did not add table 1 to uploading file by mistake. We include the table in page 18.

12. Line 119 provides the duration of follow-up range. It may also be worth adding the sample size range at this point.

# We added the range of sample size in sentence. (page 6)

13. Lines 172-177 discuss the inconsistent criterion used to define mild alcohol consumption across the studies. However, this section does not state the implications of these differences both on the findings of the individual studies and the results of the meta-analysis. The Author’s should consider these implications and present them in this section.

# We added the implication of unjustified categorization of alcohol consumption in individual study, and different criterion of mild drinking between studies. (page 9)

: Unjustified categorization of alcohol consumption might cause inaccurate result in individual studies, and different criterion on mild alcohol consumption between studies make it difficult to compare the results.

14. Line 180 - Should social factors also be considered?

15. Line 200 - Have the authors considered social and psychological mechanisms of alcohol on health?

# We think social and psychological factors is important. Those factors could be investigated by assessing which social/psychological factors affect alcohol consumption, and comparing results of alcohol use between people having different social/psychological factors. We think discussing about those factors is beyond of the methodology of this study. We will consider those factors in further
studies. Thank you for your advice.

Thank you for all valuable comments.