Author's response to reviews

Title: Preference for wine is associated with lower hip fracture incidence in post-menopausal women

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Version: 2 Date: 23 August 2013

Author's response to reviews: see over
August 23, 2013

Dear Editors,

We appreciate your thorough review and thoughtful comments. We have revised our manuscript according to your suggestions. To summarize our major changes, we have:

- Expanded the discussion of unmeasured confounding, especially with regards to socioeconomic factors
- Included reference to the 2010 Dietary Guidelines for Americans, along with a sensitivity analysis based on the guidelines
- Explored potential effect modification by study cohort and further described the differences between the cohorts
- Added an analysis of red versus white wine for a sub-cohort
- Included unadjusted models in Tables 2 and 3

Thank you in advance for your consideration of our revised manuscript. We hope you will agree that incorporation of your suggestions has led to a stronger paper. Please find below a detailed summary of the changes we have made to the manuscript.

Sincerely,

Jessica Kubo, M.S.
Biostatistician, Quantitative Sciences Unit
Stanford University

Reviewer's report

Title: Preference for wine is associated with lower hip fracture incidence in post-menopausal women

Version: 1 Date: 20 May 2013
Reviewer: Sharon Brennan

Reviewer's report:
Preference for wine is associated with lower hip fracture incidence in post-menopausal women
Kubo et al
Reviewers comments:

This study investigates associations between the consumption of different types of alcohol and hip fracture incidence in 115,655 post-menopausal women from the Women’s Health Initiative (WHI). The question has been relatively well defined. The size of the sample population is large, and various sensitivity analyses were performed. With respect, please find my concerns regarding this manuscript presented below.

Major Compulsory/Essential revisions:

Overall:

1. I query whether the associations between a preference for wine consumption and the lower incidence of hip fracture is due to the likelihood that women with higher educational attainment are those that prefer wine (data presented in Table 1), and this is the same group of women that have lower fracture incidence anyway (see for instance Brennan et al (Bone 2011) and Zingmond et al (Osteoporosis International 2006).

We agree that participants who preferred wine may differ by endogenous characteristics and that they were likely to differ based on socio-demographic factors, including education. Thank you for the suggestions of references; we have added additional references to the discussion of socio-demographic covariates and unmeasured confounding (Discussion, Paragraph 13, Line 2). We also explored the interaction of education with alcohol preference (Results, Paragraph 6, Line 6) but did not find evidence for effect modification.

2. The authors refer to ‘liquor’ throughout the manuscript, and it appears they suggest that liquor is another type of alcohol. Please clarify. Do the authors mean ‘liqueur’? Please clarify ‘hard liquor’ for non-US readers.

Thank you for pointing this out. We have clarified “liquor” to read “hard liquor” in the text.

Abstract:

3. Further information should be included in the abstract; the year of data
collection and the country from where the population were recruited.

We agree and have added this information to the abstract.

4. The conclusion should be reworded for clarity.

We have reworded the conclusion to make the findings clear.

Introduction:

5. Reference should be made to the US guidelines of moderate alcohol consumption, which state one drink per day for women (Dietary Guidelines for Americans).

Thank you for this excellent suggestion – we have added this reference (Introduction Paragraph 2, Line 3).

Methods:

6. A greater level of information regarding the WHI should be provided, especially regarding differences in the recruitment between the CT and OS cohorts, and what the interventions were in the CT cohorts.

We have included additional description on enrollment and recruitment for CT and OS and have additionally provided citations for study design and baseline monographs (Methods Paragraph 1, Line 2-4)

7. More information is required about the FFQ used – is this tool validated? Is there an appropriate citation?

We have added more information on validation in the Methods (Paragraph 4, Line 9) and Discussion (Paragraph 10, Line 4)

8. Please provide information in this manuscript concerning the ascertainment process for hip fractures, rather than stating they were “...centrally adjudicated as previously described”.

We have added details on central adjudication of hip fracture events (Methods Paragraph 5, Line 2).

Results:
9. It would be helpful for the reader if univariable associations are also presented.

Thank you for this suggestion. We have added unadjusted odds ratios to Tables 2 and 3.

10. Please make it clear what the contribution of education was to the overall model.

Education was explored as a potential effect modifier, however, we did not find sufficient evidence to suggest this was the case; the association between alcohol preference and hip fracture did not vary by education level. We additionally explored education as a potential mediator – the models that adjusted for education and that did not adjust for education showed less than half a percentage difference in point estimates for alcohol preference categories.

11. Table 1 should include the level of alcohol consumption, ie did educated women drink less (which just happened to be wine)? This issue should also be considered within the analytical model.

We explored adding amount of alcohol consumed to the model as a potential confounder; however, amount consumed was not significantly associated with incident hip fracture and did not affect point estimates for alcohol preference. This is likely due to the low level of alcohol consumption reported by this cohort. We agree that this would be an interesting issue to explore in a cohort with more variability in amount of alcohol consumed. To clarify this issue, we have added amount of alcohol consumption and category of alcohol consumption to Table 1.

12. The authors refer to a Cox Proportional Hazards (PH) model showing similar results. Given that a Cox PH is a much stronger study design, these results should definitely be shown. There is no mention made of the Cox PH methodology in the methods section.

We agree that a Cox model would have been preferable as more information could have been incorporated into the model. Unfortunately the assumptions regarding proportionality were violated and we therefore did not feel it was appropriate to present results from such a model as the validity of the findings would be in question.

13. Given that women with greater educational attainment are not only more likely to drink wine, but also more likely to have greater financial resources to undergo a hip replacement if needed, please consider a sensitivity analyses that
excluded any women with hip replacement post-baseline. This would form part of
the Cox PH.

We agree that it would be ideal to exclude women with hip replacement post-baseline, however,
this information was not collected during follow up.

14. Table 2: Consistency is required with regards to the 95%CI presented; there
are various instances where only one decimal point is provided rather than two.
We apologize for this error and have corrected the tables.

15. Were any of the women institutionalised/admitted to nursing home on a
fulltime basis at the one or three year follow ups? If so, how were these treated in
analyses? Did any of the women attend a falls prevention program during the
study period?

Unfortunately, data on nursing home admission was not collected during the main trial. While it
was collected in the extension studies, we ended follow up at main trial closeout. We also do
not have any data on fall prevention programs that participants might have attended.

16. Given different inclusion criteria between the WHI CT and OC cohorts, were
the associations shown in Table 3 similar when stratified by these two groups?
Were the interactions tested?

We tested the interaction between OS/CT cohort and alcohol preference and did not find
evidence of effect modification. When we stratified the analysis by OS/CT cohort, the point
estimates for wine preference remained in the same direction as the main analysis of CT/OS
combined in each of the cohorts.  (Results Paragraph 6, Line 7)

Results/Discussion:

17. Please clarify the categories of Wine (yes vs no) presented in Table 3. I.e,
does the ‘no’ group include those that consumed other types of alcohol? (The
title of this table requires clarity). If the ‘no’ group does include other alcohol
consumers, is it possible that they could be something in this group that
increased the likelihood of fracture, rather than those who consumed wine having
a reduced risk of fracture? The authors themselves allude to this possibility in their abstract background when referring to the different components of alcohol types and the differential influence on hip fracture. Also, were the differences inherent in red vs white wine considered?

We have clarified in the text that these categories are not mutually exclusive. (Methods Paragraph 4, Line 3) We agree that it is important to consider alcohol consumption from wine, beer and hard liquor separately, which is the reason for also considering the mutually exclusive categories of alcohol preference. To address whether the reduction in risk for those who prefer wine is due to red or white wine, we have added a sub-analysis of OS participants who had follow up data at year 3. We did not find a significant association between alcohol preference with wine categorized into red wine, white wine, or both in this cohort. (Results Paragraph 6, Line 8)

18. One or more serving of alcohol (regardless of type) is a cut point that refers to moderate alcohol consumption according to US standards. Do the statistical associations hold when categorising alcohol consumption as two or more glasses per day, especially given that the Dietary Guidelines for Americans suggest that consuming more than the moderate amount of alcohol (ie two or more) increases the risk of injuries from falls. This is an important issue to consider when investigating alcohol consumption in context of fracture risk (Vestergaard et al, Scandinavian Journal of Public Health, 2006), and associations between falls and socioeconomic status (West et al, Public Health 2004).

This is a great suggestion. Although very few women in this cohort consumed more than two servings of alcohol per day, we added a sensitivity analysis defining alcohol consumption as more than one serving per day in concordance with the DGA’s definition of moderate consumption as up to one serving per day. Although not significant, point estimates were in the same direction as the analysis defining alcohol consumption as more than one serving per week (Results Paragraph 7, Line 4).

19. The authors make a brief mention in their limitations section that wine drinkers may differ by other characteristics that could include incident fracture.
This is an important point and worthy of greater discussion. For instance, Farahmand et al (Osteoporosis International 2000) observed that whilst educational attainment was not associated with hip fracture in women, employment, income, type of housing and marital status were significantly associated with hip fracture independent of other risk factors.

We agree that the issue of confounding by socioeconomic factors is important to address, and have added to the discussion of unmeasured confounding (Discussion Paragraph 13, Line 3-4). Thank you for the suggested references – we have included citations to these and others.

Authors contributions:

20. Please clarify whether all authors approved the final version of this manuscript for submission.

Thank you for pointing this out. We have added a statement to the author contributions section.

Discretionary revisions:

Title:

21. The title is slightly misleading, as it refers to a ‘preference for wine’, but does not indicate a comparator.

In addition to the model of alcohol preference using non-drinkers as the reference group, we also fit a model of alcohol preference using those who prefer wine as the reference group and found that wine drinkers had a reduced risk of hip fracture compared to beer drinkers, hard liquor drinkers, current drinkers with no strong preference, past drinkers, and non-drinkers. (Results Paragraph 3, Line 3) Since the only other group was the current infrequent drinkers, we chose not to name the comparator groups in the title.

Results:

22. Figure 1: Please clarify what ‘form’ means, in the box labelled ‘Excluded due to missing form’.

We have clarified exclusions due to missing forms as being due to missing survey instruments in Figure 1 and in the text.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.
Reviewer's report

Title: Preference for wine is associated with lower hip fracture incidence in post-menopausal women

Version: 1 Date: 19 July 2013

Reviewer: Shinya Ishii

Reviewer's report:

This study confirms and extends previous studies that have found association between preference for wine and lower risk of hip fracture risk in postmenopausal women. The findings are of some interest and may lead to further research to determine the underlying biological mechanisms of the protective effect of wine.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests

Response: Thank you for your review.