Author's response to reviews

Title: Alcohol intake, wine consumption and the development of depression: The PREDIMED study.

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Version: 2 Date: 2 July 2013

Author's response to reviews:

Dr. Sabina Alam
Editor-in-Chief,
BMC Medicine
Pamplona, July 2nd, 2013

Dear Dr. Alam:

We are pleased to submit a revised version of our manuscript entitled “Alcohol intake, wine consumption and the development of depression: The PREDIMED Study” that you considered as potentially acceptable for publication in BMC Medicine.

Please find below a point-by-point answer to each of the comments and issues raised by the reviewers.

We look forward to your comments and decision on our contribution in due time.

Sincerely,
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Please find below a point-by-point answer to your queries. All changes and additions in the new version of the manuscript are written in red font.

Reviewers’ comments

Reviewer 1
I would have liked more detail on the data collection, but presumably this has been presented in other papers on the intervention study.

Thank you for your interest: in this paper we only briefly describe the protocol of the trial. However we cited the cohort profile paper (reference 22) and the main results of the trial (reference 23), where all this information is publicly available (both articles are free for public download). Moreover, we also mentioned the website of the trial (www.predimed.es) where additional information and open access materials are available.

Similarly, the language could have more concise in parts of the manuscript.
We have revised the manuscript to make it more concise.

Finally, I did not find the figure very helpful – how many in the sample drank 50-80 g per day?
In our sample, few participants could be considered heavy drinkers. In fact, only 147 participants drank between 50 and 80 g/day. Our cohort offered a unique opportunity to investigate the influence of two particular factors: light-to-moderate drinking and wine consumption. This is so because the prevalence of low-to-moderate average alcohol intake was very high, whereas the prevalence of excessive drinking was very low. In addition a strong preference for wine consumption was present in this cohort. We mentioned these features in the text. We also acknowledged that these circumstances limited our power to detect specific associations between heavy drinking and depression. So the figure may suggest heavy drinkers may be at higher risk, and it reflects adequately the protection found for moderate drinkers. We have included some of these considerations in the discussion section.

Reviewer 2
1. Sample exclusions: For reasons that are not explained, the study excludes 1579 participants who reported baseline depression or a history of depression. I can see no good reason for excluding these participants and a better approach would have been to include all cohort members and use prior history of depression as a covariate in statistical models.
This is a very interesting point. We excluded participants who reported a previous
history of depression because these patients with previous depression are more prone to develop a new episode of depression, or to be recurrent cases. Moreover prior depression may change dietary habits and more specifically alcohol intake. Therefore we considered that to include participants with previous depression may introduce a potential bias. For these reasons, in cohort studies it is customary to exclude participants who had already developed the outcome at baseline. We did so. Concretely, this inclusion may introduce a reverse causation bias, and we decided to use restriction to eliminate this source of bias. As we mention above, this is the common practice in all cohort studies, also in those investigating depression (see for example: Arch Intern Med. 2011;171:1571-8). We have included this information in the revised version. Moreover, we have included as a sensitivity analysis the results of Cox regression model including participants with history of depression at baseline and using prior history of depression as a covariate.

2. Measurement of Alcohol Exposure: The study represents alcohol use in the sample using a highly truncated distribution in which the highest alcohol consumption group is > 15 grm per day. This category includes 20% of the sample. This truncation of the alcohol distribution limits the capacity of the study to detect effects of heavy drinking on depression. Further as shown in figure 1 a cubic spline analysis with a less restricted range of alcohol consumption suggests a curvilinear relationships in which moderate drinking up to about 40 grams per day is either beneficial or not harmful whereas after that point risks increase. This finding is obscured by the truncated range used in the main analysis and is not mentioned in the paper or abstract. It is my view that the authors need to revise the paper to develop a more sensitive measure of alcohol use which ranges from none to very heavy drinking.

As we mentioned in the discussion section of the manuscript, few participants in our sample are heavy drinkers. This is to be explained because candidates with problematic alcohol use were not eligible for inclusion in the trial. This fact may limit our power to detect any effect of heavy drinking on depression incidence. However, the results in the spline analysis do suggest an elevated risk for depression among heavy drinkers. To go deeper into your suggestion, we re-categorized alcohol intake in 5 categories: Abstainers, 0-5 g/day, 5-15 g/day, 15-40 g/day, and >40 g/day. Participants in the category of >40 g/day (n=237) were at higher risk of depression compared with abstainers, however this association was not statistically significant: HR (95% CI) = 1.34 (0.69-2.59). Taking into account the width of the confidence interval, we believe that this lack of significance can be potentially related to low statistical power. Even though the point estimate for the comparison of participants who consumed >40 g/day versus abstainers suggested a higher risk of depression among heavy drinkers, the confidence interval was wide, most likely due to a small number of participants in this category (>40 g/day). This is a small number and estimations will be unstable. However, as happened with the spline analysis, these results suggest that heavy drinkers will be at higher risk of depression. This finding is in accordance to previous studies, however we do not have enough power to achieve a precise and stable estimation of the relative risk of depression of heavy
drinkers. As we were aware of this limitation, we had focused our aims in evaluating the incidence of depression among light to moderate drinkers. We have included these results in the text. We have also modified the conclusion in the text and in the abstract, and added our potential limitation of statistical power to detect effects among heavy drinkers.

3. The measurement of depression is also limited by the use of physician reports since most people with depression do not go to their doctor. The use of measures of physician consultation potentially introduces biases into the study as a result of the possibility that patterns of alcohol consumption may be associated with decisions to seek care. This could result in the rates of depression being underestimated for heavy drinkers.

Thank you for your comment. We have included this consideration as a limitation in the discussion section of the new version of the manuscript.

4. Control for confounding: The authors do a generally good job of controlling for confounding factors. However given that the study has repeated measures data a far better way of addressing confounding may be to fit a fixed effects regression model to the repeated measures data. As explained in reference 29 it is possible with repeated measures data to control for non-observed fixed sources of confounding using the fixed effect regression model.

This is a very interesting suggestion. In our study we hypothesized that moderate alcohol intake may reduce the risk of developing depression. According to that hypothesis we defined a cohort of participants at risk who did not have a diagnosis of depression at baseline and also did not use antidepressant drugs at study inception. We then observed the incidence of depression in this cohort. During follow-up, 443 participants were classified as incident cases of depression, that is, 8% of the total sample. Fixed effects regression model is a very useful tool to control for intra-subject non-variant sources of confounding, both the observed and the non-observed ones. Thus, the study of variation within a person is a strength of this model. However fixed effects models include only subjects who change their outcome during the follow-up period, therefore the estimation found with this technique will be based on 8% of observations. On the contrary, 92% of observations will not be used (92% of participants were not depressed at baseline and did not develop depression during follow-up). Since there is too little intra-subjects variation in outcome, fixed-effects models will result in very unstable estimations or even in non-convergent models.

To solve this problem we decided to investigate another hypothesis: alcohol intake may influence the incidence of, the recurrence of, and the recovery from depression. Then we start with all participants, depressed or not at baseline, and observed either the incidence of depressive episodes (new cases or recurrent cases), or the recovery from a depressive episode. In this scenario, a fixed-effects model uses almost 30% of our subjects and the models converge. These participants are those who become depressant or recover from depression during follow-up.
Abstainers >0-5 g/day >5-15 g/day >15 g/day

Crude 1 (Ref.) 0.98 (0.83-1.17) 0.92 (0.73-1.16) 0.87 (0.62-1.22)
Age-adjusted model 1 (Ref.) 0.91 (0.66-1.06) 0.84 (0.66-1.06) 0.76 (0.54-1.07)
Multiple-adjusted model 1 (Ref.) 0.91 (0.76-1.08) 0.86 (0.67-1.09) 0.76 (0.53-1.09)
We included these results as a new additional table.

5. Reverse Causality: The authors argue that their findings suggest that moderate alcohol consumption leads to reduced risks of depression. However, it is possible that this association arises from reverse causal association in which a healthy state of mind is associated with moderate alcohol consumption. For these reasons the paper needs to include some examination of reverse causation. Again reference 29 outlines a way of doing this with repeated measures data.

Potential reverse causation bias is a very important concern when studying the relationship between alcohol intake and depression status, since relationships in both directions have been described in the literature. Since we were aware of that, we made some efforts in the design of our study to avoid this bias because we were interested in appraising the association in the direction from alcohol to depression and not vice-versa. First of all, we excluded participants with prior history of depression. Prior depression may lead to changes in dietary habits and more specifically in alcohol intake. Moreover, when we used repeated measures analysis, we established an induction period of 1-2 years to ensure the temporal sequence. Also, as sensitivity analysis, we lengthened this period to 2-3 years to be even surer that alcohol intake precedes depression. In these two analyses, results were consistent, so reverse causation bias seems not to be biasing our results.

Our interest focused on the primary prevention of depression. However, we could additionally explore what is the role of depression on the alcohol consumption pattern once a participant has already become depressed, compared with participants who did not become depressed:

There were no statistically significant differences in changes in alcohol intake [g/day (95% CI)] between incident cases of depression and the rest of the cohort in the crude, sex- and age-adjusted, and multiple-adjusted models; [0.49 (-0.77, 1.76); 0.11 (-1.16, 1.38); 0.06 (-1.21, 1.33)]. Since the incidence of depression seems not to change alcohol intake in our population, our results are more likely to be free of reverse causation bias.

However, an alternative explanation for the observed association is that wine-drinkers or moderate drinkers are healthier in other aspects than non-wine drinkers or non-moderate drinkers, as suggested by the reviewer. In order to account for confounding by these factors, several lifestyle variables, including quality of the diet and several indicators of an overall healthy lifestyle and health consciousness had been included in the multiple-adjusted model. We have included this explanation in the new version of the manuscript.