Reviewer’s report

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

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Reviewer: David Fergusson

Reviewer’s report:

This paper uses data from the PREDIMED study to examine the linkages between alcohol consumption and depression in a high risk elderly sample. The paper reaches the interesting conclusion that moderate alcohol use was associated with reduced risks of depression. While the findings of this study are interesting, the study design and analysis have a number of features that raise concerns about the validity of the interpretation of the data. These concerns are:

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.

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 relationship 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.

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 under-estimated for heavy drinkers.

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,
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.

In summary, while the findings of this paper are interesting the paper requires major revisions. In my view the compulsory revisions include:

i) analysing the full sample rather than excluding the 1579 participants who reported prior depression.

ii) Changing the classification of alcohol consumption to permit examination of the risks of depression with alcohol consumption over a range from no drinking to very heavy drinking. If the cubic spline analysis shown in figure 1 is correct this should lead to the conclusion that: moderate drinking is associated with modest reductions in risks of depression whereas heavy drinking lead to increased risks of depression.

Optional revisions which would improve the paper include:

i) the used of fixed effects regression to control associations between alcohol use and depression for non-observed sources of confounding.

ii) The use of structural equation modelling methods to test for reverse causality.

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I have no competing interests