Author's response to reviews

Title: A longitudinal assessment of alcohol intake and incident depression: The SUN Project

Authors:

Alfredo Gea (ageas@alumni.unav.es)
Miguel A Martinez-Gonzalez (mamartinez@unav.es)
Estefania Toledo (etoledo@unav.es)
Almudena Sanchez-Villegas (asanchez@dcc.ulpgc.es)
Maira Bes-Rastrollo (mbes@unav.es)
Jorge M Nuñez-Cordoba (jnunezco@unav.es)
Carmen Sayon-Orea (msayon@alumni.unav.es)
Juan J Beunza (jjbeunza@unav.es)

Version: 2 Date: 29 August 2012

Author's response to reviews: see over
Pamplona, August 28th, 2012

Dear Dr. Natalie Pafitis,
Executive Editor- BMC Public Health

We are pleased to submit a reviewed version of our manuscript entitled “A longitudinal assessment of alcohol intake and incident depression: The SUN Project” that you considered as potentially acceptable for publication in *BMC Public Health*.

Please find below the point-by-point answers to all the comments and issues raised by the reviewers.

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

Sincerely,

Prof. Miguel A. Martínez-González, MD, PhD, MPH
Chair, Dpt. Preventive Medicine & Public Health, Univ. of Navarra
IRUNLARREA 1. 31008 PAMPLONA, SPAIN
Tel: +34-948-425600 (Ext 6463); +34-636355333
mamartinez@unav.es
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

2. Are the methods appropriate and well described?

The recruitment period is not clearly stated: “Up to February 2008, 19,576 subjects were recruited.” When did recruitment begin?

This information was only in the abstract and we agree it should also appear in the text. The recruitment started in 1999. We have included this information in the revised version.

The way retention was measured is not clearly described: “Of these, 17,462 were successfully followed-up, achieving a retention rate of 89.2%.” How was “successfully followed-up” defined? At least one follow-up? More than one?

Thank you for your suggestion. We considered successfully followed-up any participant who responded to at least one follow-up questionnaire. We have clarified it in the text.

Alcohol consumption was assessed at baseline by questions on type of alcohol and quantity per day. What is the time period for baseline alcohol consumption? Past week? Past month? How was episodic drinking defined? For example, how were participants who drank large quantities once per week classified?

The time period is one year as it is usually done in dietary assessments with Food Frequency Questionnaires (FFQ) (Willett W, Stampfer M. Food-Frequency Methods. In Nutritional epidemiology. 2nd edition. New York: Oxford University Press; 1998:81). Alcoholic beverage consumption was assessed through a validated FFQ. This FFQ included questions about red wine, non-red wines, beer, and liquors, and it inquired about the past year average consumption of each beverage. With this information we calculated total daily alcohol intake. We have improved the description of the FFQ in the text. In the present paper we did not consider patterns of consumption, but only daily alcohol intake. The National Institute of Alcohol Abuse and Alcoholism (NIAAA) defines binge drinking as the consumption of 5 and 4 drinks per occasion for men and women respectively (NIAAA council approves definition of binge drinking. NIAAA Newsletter 2004; No.3, p. 3. Available at http://pubs.niaaa.nih.gov/publications//Newsletter/winter2004/Newsletter_Number3.pdf Accessed August 24, 2012). Binge drinking was seldom present in our participants. Only 4 participants drank 4 or more spirits/day (not per occasion) and only 11 participants drank 4 or more beers/day (not per occasion). Therefore, our study was unable to assess the association between binge drinking and depression. On the other hand a strength of our study is related to the low average alcohol consumption which give us a good scenario to obtain conclusions about low-to-moderate levels of consumption. Future studies that can include a sufficient number of patients with very high alcohol consumption or exposed to binge drinking can assess the effects of those
exposures.

Incident cases of depression were identified by a positive response to the question, “Have you ever been diagnosed of depression by a medical doctor?” or a positive report after 4 or more years of follow-up habitual use of antidepressant drugs.” Research suggests first treatment for depression typically occurs several years following the onset with the median time from onset of depression to first treatment reported as 8 years in the U.S. population (Wang et al., Arch Gen Psychiatry. 2005;62:603–613). Long lags in first contact for depression treatment have also been reported in other countries (Olfson et al., Med Care. 2012 Mar;50(3):227-32). Thus, identifying incident cases of depression by having received a diagnosis or prescribed medication by a medical doctor may result in missed cases. This is especially true for cases recruited later in the study who were followed up for a shorter period of time than case recruited earlier in the study.

Thank you for your comment. We have included this consideration in the discussion section of the new version. Missed cases would mean that some patients were classified as healthy when they really had depression; that is they would be “false negatives”. This may lead to a reduced sensitivity for our definition of incident depression. However our definition is not likely to lead to many “false positives” (basically all patients classified as “depressed” were true positives). Therefore a very high specificity is expected for our case definition. This implies that almost every participant classified as incident case of depression is really a case of depression according to our validation study. A specificity of 0.96 was obtained in the validation study of the depression assessment, at the expense of sensitivity. Therefore we agree that some cases of depression will not be identified by our assessment. However we are more interested in obtaining a very high specificity because, theoretically, with perfect specificity, non-differential sensitivity of disease misclassification will not bias the relative risk estimate (Greenland S, Lash TL. Bias analysis. In: Rothman KJ, Greenland S, Lash TL, Eds. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2008:359.).

3. Are the data sound?

The authors considered a number of potential confounders in their adjusted model: smoking, physical activity, total energy intake, body mass index, adherence to the MDP, marital status, and employment status. They did not consider illicit drug use or abuse of medications, which is strongly associated with depression.

In the sensitivity analyses, prevalent cases of other psychiatric disorders and conditions (insomnia, schizophrenia, anxiety, anorexia and bulimia, stress, obsessive compulsive disorder, bipolar disorder, phobias) at baseline were excluded. Prevalent cases of drug dependence, which is also strongly associated with depression, were not excluded.

We appreciate your comment. However, unfortunately we did not have any information about illicit drug use in the SUN cohort. Despite this limitation, it should be considered that the SUN cohort participants are university graduates who voluntarily agreed to complete very long and complicated questionnaires. Thus they are health-conscious and responsible subjects. In this context we expect that the use of
illicit drugs in this population will be very low or even non-existent. We have included this potential limitation of our study in the discussion of the new version.

On the other hand we do have information about prescribed psychiatric medication use. To comply with your suggestion we have conducted additional sensitivity analyses after excluding psychiatric medication at baseline and during follow-up. Please find below a table containing the results of the Cox Regression analyses. Hazard Ratios and 95% Confidence Intervals were calculated according to alcohol intake categories, using the Abstainers group as the reference category.

As shown in the table, results did not significantly change after excluding patients under psychiatric or other medication. We have included these analyses in the text as additional sensitivity analyses.

<table>
<thead>
<tr>
<th>Sensitivity Analysis</th>
<th>Abstainers</th>
<th>0-5 g/day</th>
<th>5-15 g/day</th>
<th>&gt;15 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>After excluding participants under anxiolytic medication use at baseline</td>
<td>1 (Ref.)</td>
<td>0.98 (0.77-1.24)</td>
<td>0.65 (0.48-0.87)</td>
<td>0.77 (0.53-1.14)</td>
</tr>
<tr>
<td>After excluding participants under anxiolytic medication and other psychiatric medication use at baseline</td>
<td>1 (Ref.)</td>
<td>1.08 (0.82-1.41)</td>
<td>0.70 (0.50-0.98)</td>
<td>0.90 (0.60-1.37)</td>
</tr>
<tr>
<td>Excluding participants under anxiolytic drug use during the follow-up period</td>
<td>1 (Ref.)</td>
<td>0.91 (0.70-1.18)</td>
<td>0.65 (0.47-0.89)</td>
<td>0.70 (0.45-1.06)</td>
</tr>
<tr>
<td>Excluding participants under antiepileptic and anticonvulsant drug use during the follow-up period</td>
<td>1 (Ref.)</td>
<td>0.95 (0.75-1.21)</td>
<td>0.67 (0.50-0.90)</td>
<td>0.79 (0.54-1.15)</td>
</tr>
<tr>
<td>Excluding participants under antipsychotic drugs use during the follow-up period</td>
<td>1 (Ref.)</td>
<td>0.97 (0.77-1.23)</td>
<td>0.65 (0.49-0.87)</td>
<td>0.75 (0.52-1.10)</td>
</tr>
</tbody>
</table>

6. Are limitations of the work clearly stated?
If data on illicit drug use or abuse of prescribed medication was not collected in the SUN study, this should be stated.

We agree and we have included this as a limitation for illicit drugs use. With respect to prescribed medication, we do have information about it and we have conducted some additional sensitivity analyses. This has been included in the new version of the manuscript.

The issues related to measurement of alcohol use and depression stated above in #2 may be limitations. If so, this should be stated.

Thank you for your comment. We have included some comments about these potential limitations in the discussion.

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

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

We have edited the manuscript to try to improve the quality of written English.

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.