Author's response to reviews

Title: Alcohol use disorders and risk of Parkinson's disease: findings from a Swedish national cohort study 1972-2008

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Author's response to reviews:

We are very grateful for the comments made by the reviewers. We have responded to them point by point, please see below.

Reviewer's report
Title: Alcohol use disorders and risk of Parkinson's disease: findings from a Swedish national cohort study 1972-2008
Version: 1 Date: 27 September 2013
Reviewer: Natalia Palacios
Reviewer's report:

Major Compulsory Revisions:

Models need to adjust for smoking if you're looking at Alcohol and PD.

Answer: We totally agree with the reviewer and wish that we would have had the possibility to adjust for smoking. However, smoking habits are not recorded in the Swedish inpatient register. The obvious reason why we use register data from a national cohort is to reach a sufficiently large sample to study Parkinson's disease, and also to be able to study chronic alcohol consumption by means of diagnoses of alcohol use disorders. We are aware of, and are mentioning in the Discussion, the second paragraph (page 8), that there is fairly robust evidence demonstrating an inverse relation between current-smoker status and incidence of Parkinson's disease – that is, tobacco smoking appears to attenuate the risk of developing Parkinson's disease (see for instance Noyce et al, 2012). With this in mind – as well as that current tobacco-use prevalence may approach 75% among individuals seeking treatment for alcohol-related problems – it is likely that our lack of adjustment for tobacco smoking actually leads to an underestimation of the risk between chronic alcohol consumption (alcohol-use disorders) and the development of Parkinson's disease.

Like you mention in the discussion, it is good to adjust for number of hospital
admissions to account for healthcare utilization.

Answer: We can understand the point made by the reviewer. However, to do this we would have to adjust for the total amount of admissions for all diagnoses, and we only have information on admission for alcohol related disorders, appendicitis and Parkinson’s disease.

In Table 2, not clear what the different models adjust for - model 2 and 4 both say only age at exposure. Are all the models adjusting for sex, if not why not?

Answer: We thank the reviewer for pointing this out. Model 4 is adjusted for both age at exposure and sex. This information had accidently been dropped out from the manuscript.

Another factor good to adjust for is NSAID use, as it theoretically could be used to treat alcohol-related symptoms (aka hangover) and is related to PD.

Answer: Unfortunately we did not have the possibility to adjust for NSAID use. However, it is likely that our lack of adjustment for NSAIDs resulted in an actual underestimation of the risk of Parkinson’s disease for alcohol-use disorders.

My main concern with the study is the case selection. It seems to use a very broad definition of PD from the national register. I would like to see results for PD only. For example, ICT-8: 342 was included which includes Parkinsonism, a condition different from PD. There have been reports of symptoms of Parkinsonism provoked by alcohol abuse and withdrawal, but this is different from Parkinson Disease. This is an important issue that needs to be addressed in the analysis and discussion, if you are trying to focus a study on the role of alcohol in Parkinson Disease.

Answer: We are sorry if we have expressed ourselves unclear on this matter. As for the ICD-9 332A and ICD-10 G20 codes they are very specific for Parkinson’s disease and are not meant to identify any neurological condition other than Parkinson’s disease. However, we thank the reviewer for drawing our attention to the ICD-8 codes where we now have restricted the analysis to 342.00 which captures only Parkinson’s disease, and excluded 342.08 (other defined parkinsonism) and 342.09 (unspecified parkinsonism) that previously by mistake were included in the analyses. By doing this, the number of PD cases is slightly reduced (with 20 cases), and we have recalculated all our estimates. However, the results were essentially the same.

We have rewritten the sentence in the manuscript describing this, as follows (page 6) under the heading Classification of PD: “First admission with a diagnosis of PD registered in the Swedish National Inpatient Register was defined according to the Swedish version of the eighth (ICD-8), ninth (ICD-9) and tenth (ICD-10) revisions of the WHO International Classification of Diseases, with
the following codes: ICD-8: 342.00; ICD-9: 332A; and ICD-10: G20.”

We have also added information describing which individuals were excluded from our cohorts, in the second paragraph under Methods, Study population (page 4 and 5): “Individuals were excluded if they belonged to one or more of the following groups: 1) had been hospitalized with a diagnosis of PD prior to or concurrent with admission for an alcohol use disorder or appendicitis, n=630; 2) had been hospitalized with a diagnosis of Parkinsonism (diagnostic codes ICD-8: 342.08 and 342.09; ICD-9: 332B and 333A-X; or ICD-10: G21-G26) prior to or concurrent with admission for an alcohol use disorder or appendicitis, n=146;”

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: Alcohol use disorders and risk of Parkinson's disease: findings from a Swedish national cohort study 1972-2008
Version: 1 Date: 29 September 2013
Reviewer: Cristian Falup-Pecuraru
Reviewer's report:
Minor revision.
This is a nice paper with a robust methodology which is evaluating 37 years of a strong database in Sweden.
I will ask the authors to compare the mean age of group of appendicitis and alcohol users and comment of it.

Answer: This is an important point made by the reviewer. We have added information on mean age of the cohorts to the results section, first paragraph (page 7), as follows: “The mean follow-up time was 13.6 years for the group with alcohol use disorders and the mean age at exposure 43.0 years. In the group with appendicitis the mean follow-up time was 17.1 years and the mean age at exposure 30.0 years.”

We have also added the following in the Discussion section, second paragraph (page 8):

When adjusting the estimates for age, the HRs were reduced. This can be explained by the difference in mean age of admission for the two exposure groups in our study; the mean age of first admission with an alcohol use disorder
was higher. I.e. the group with alcohol use disorders was admitted to inpatient care later in life, although their alcohol abuse most probably have started much earlier, compared to the group with an appendicitis, for which patients are admitted immediately, and at a younger age.

Level of interest: An article of importance in its field
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.