Dear Dr. Topiwala

Manuscript ID BMJ.2016.034088 entitled "Moderate alcohol consumption as a risk factor for adverse brain outcomes: a 30-year prospective cohort study"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Dr. Wim Weber
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**Report from The BMJ's manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: José Merino (Chair), Jon Deeks (Statistics advisor), Jessamy Bagenal, Elizabeth Loder, Amy Price, Tiago Villanueva, Wim Weber.

Decision: Put points

Detailed comments from the meeting:

We thought your paper addresses an interesting and important research question. We had the following concerns:

We thought your paper addresses an interesting and important research question. But after discussion we felt that it did not add enough to take it further towards publication in The BMJ. We had the following concerns:

The main drawback is that there are no baseline scans. As 2 of the reviewers point out, this limits the ability to draw any firm conclusions about the association.

You have used factor analysis to reduce cognitive tests down to a smaller number of variables. This was done on the data collected and thus will have added a degree of "data dredging" type bias, but we also could not grasp quite what the outcome variable you are looking at actually measures.

In the end it is very unclear what conclusion can be drawn about alcohol consumption and cognitive function from the data that you have presented, as it does not independently predict.

There is no detail of how random sample was chosen.

There are no raw data presented.

Outside the UK it is not common to categorize alcohol intake by "units". This should be described through examples early in the paper. Perhaps a box would be helpful, along with a link to the NHS website calculator that allows people to calculate how many units of alcohol are in a glass of wine, can of beer, etc.

Could this be put in a more international context? The authors discuss this in terms of NHS recommendations but it would not be difficult to reference US guidelines and definitions of moderate drinking.

In the WTSA box you say you show moderate alcohol use is associated with an increased risk of LATER adverse brain outcomes. We don't think you can make that temporal claim if you don't have baseline scans.

There are many technical details given on the image processing methods, which needs a simple summary produced.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.
In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

Topiwala and colleagues aimed to examine the relationship between alcohol consumption and brain structure and function in a relatively large study population. The advantage of the study includes a repeated measure of alcohol intake over a long period of time, multiple brain structural measures, and SEM analysis of the relationship between alcohol, brain, and cognition. The manuscript was well written, and the findings on alcohol and white matter microstructure is novel. The paper would benefit from a more thorough review of the literature on the research topic, a reduced number of tables and figures, and more discussion on whether the findings meet the authors’ hypothesis and why alcohol was negatively associated with brain.

Page 4 “Increased alcohol consumption over the 30-year follow-up was associated with increased odds of hippocampal atrophy in a dose dependent fashion.” is confusing. Consider change the word ‘increased’ into ‘more’ as ‘increased” implies a longitudinal analysis of alcohol consumption but the analysis was based on average intake.


The % of subjects in the ‘unsafe’ category in table 4 seems to be high. How are these numbers compared to other studies?

There are too many tables and figures. The authors may want to consider reducing the numbers of table or figures.

In table 6, please give number of subjects for each drinking categories.

Strictly speaking, the analysis is not a prospective one as the baseline brain status was not available so no longitudinal data on the outcome side.

It will be great if more detailed information regarding the longitudinal change of alcohol intake is presented. Which factors are associated with change in addition to baseline intake level? Also, line 26 on page 31 said “Additionally, drinking habits were remarkably stable over a 30-year period”. Yet the table 4 showed clearly there are some changes in alcohol consumption over time and the mixed effects model showed increase in intake (see page 25, line 21: Weekly alcohol intake increased over the phases of the study (β=0·22, CI: 0·05 to 0·4, p<0·01).

It will be interesting to examine whether baseline alcohol itself is related with brain structure.

More discussion is needed on whether the findings meet the authors’ hypothesis and why alcohol was negatively associated with brain.

Additional Questions:
Please enter your name: Yian Gu

Job Title: Assistant Professor

Institution: Columbia University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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Recommendation:

Comments:

This is a large study addressing an important clinical issue, namely is alcohol intake at non-dependent leaves associated with brain structural abnormalities. The main finding is that moderate and high users of alcohol had reduced hippocampal grey matter density/smaller hippocampal volume and differences in corpus callosum microstructure compared to those who abstained or had low intake. Assessment of the relationship between alcohol use and brain structure is only undertaken in a cross-sectional manner, but there is assessment of alcohol use over several time points. A dose response relationship is seen between level of alcohol intake and hippocampal volume loss. The finding that light alcohol use does not confer protective effects to the brain has important public health implications.

Strengths of the study are obviously the fact that alcohol consumption is assessed prospectively, numbers are large and DTI as well as volumetric and density assessments are undertaken. Automated approaches are used to ascertain structural volumes. While not the goal standard of manual segmentation, given the number of scans being assessed this approach seems reasonable to me.

The major weakness of the study is that whereas there may be longitudinal data on alcohol use, the imaging component of the study is cross-sectional. This means that there is a very real possibility that a ‘third factor’ underpins the association between alcohol use and imaging abnormalities, rather than these abnormalities arising as a consequence of alcohol use. It has been suggested for example that impulsivity and impulse control disorders such as gambling are associated with smaller hippocampal volume, (Raman et al, Zetzsche et al) and greater impulsivity would be expected to be associated with greater alcohol use. Similarly, corpus callosum abnormalities have been reported in alcohol-naive adolescents at high familial risk of alcohol use (Venkatasubramanian et al). It is hard to see how the possibility of a ‘third factor’ underpinning the association can be excluded given that though data on alcohol use was collected at several time points, imaging was only done at one time point; consequently we can’t be sure that these imaging findings do not represent trait differences. I think this weakness needs to be highlighted/discussed in more detail in the paper.

The key to addressing the above issue is of course to obtain brain imaging at different time points, so it can be established if structural changes do occur in association with alcohol use. One would expect however that, if the association was causal, given that lower hippocampal volume was associated with poorer cognitive performance, one would see a greater decline in cognitive performance over time in the heavy drinking group than controls. Some cognitive testing was done at timepoint 7 as well as at the time of scanning, so this may be possible to ascertain. I appreciate however that if only the MMSE was done at timepoint 7, then this may be too blunt an instrument to detect any change. If this is the case it is a shame. Was any more detailed assessment of cognition undertaken at the time of initial recruitment?

It is reported that hippocampal volumes were ascertained using the automated approach FIRST. I cannot however see these data in any of the tables, and they are not discussed in the results section. I think it is important to display these results; the reader must know if they are compatible with findings from the brain-wide voxel-based approach and clinical visual ratings of hippocampal atrophy.

Minor Issues

Page 5: Moderate alcohol consumption (defined as >15 units (120g) / week) in older subjects was associated with grey matter atrophy11 and reduced frontal and parietal grey matter density. My reading of the Kubota paper (reference 16) however is that frontal atrophy (indicated by widening of the CSF space, not based on measurement of volume of grey matter) was only seen at average levels of alcohol consumption of 418g per week, or around 52 UK units. Though it is reported that in a subanalysis results are adjusted for ‘baseline’ cognitive function, this is actually cognitive function at phase 7 (mean age 59), when participants had already been in the study for around 15 years, and will presumably already have had substantial exposure to alcohol. According to Table 5, none of the participants in the study were smokers. This seems rather surprising, as it doesn’t seem smokers were actively excluded. Can the authors explain how this has occurred/comment on why?

It seems from this study men are more prone to exhibit hippocampal atrophy in association with alcohol use. This is a rather surprising finding, as previous studies have suggested the brains of women are more vulnerable to the effects of alcohol. Does this fit with the possibility that the association between levels of alcohol use and smaller hippocampal atrophy may not be causal (i.e. men have a greater loading for a third factor which is associated with both smaller hippocampi and alcohol use)? Could the finding that alcohol use did not directly predict cognitive function also fit with the possibility that the association is not causal (i.e. smaller hippocampal volume is associated with poorer cognitive performance and increased risk of alcohol use)?


Additional Questions:

Please enter your name: Killian Welch
This is a very interesting study reporting a previously unrecognised association with units of alcohol use, hippocampal atrophy and cognitive abnormalities with moderate alcohol use. Considerable strengths of the study are the large number of subjects, long follow up period before scanning, use of popular clinical ratings as well as contemporary neuroimaging methods and neuropsychology, attention to potential confounders, plus finding a dose effect relationship.

I think it is very suitable for publication and so I have only a few minor suggestions to help improve the text.

P20 Fig 4 The abnormal regions shown include the hippocampus but also appear to extend more anteriorly into the amygdala. It would be helpful to clarify localisation and add comments to the discussion on the amygdala if appropriate. (Preclinical models of alcohol misuse have also implicated the amygdala, e.g. Koob).

P6 history of MDD assessed by structured clinical interview for DSM IV at the time of the scan. Is this a history of current illness at the time of assessment or any episode of MDD preceding assessment?

P11 Various different definitions are used throughout the manuscript regarding drinking habits: e.g. safe vs unsafe drinking, abstinent, mild, moderate, etc. In p11 there is a list of the different ranges <1, 1-7, 14-20, 21-30, >30 units that have been used. It would be helpful to summarise these definitions in the 'Study Design' section.

P11 calculation for potentially confounding variables. How was history of MDD quantified for covariate analysis and in particular how was 'current psychotropic medication' quantified for correction?
Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

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