Author's response to reviews

Title: The association between delusional-like experiences, and tobacco, alcohol or cannabis use: a nationwide population-based survey.

Authors:

- Sukanta Saha (sukanta_saha@qcmhr.uq.edu.au)
- James G Scott (James_G_Scott@health.qld.gov.au)
- Daniel Varghese (Daniel_Varghese@health.qld.gov.au)
- Louisa Degenhardt (louisa@burnet.edu.au)
- Tim Slade (tims@unsw.edu.au)
- John J McGrath (John_mcgrath@qcmhr.uq.edu.au)

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Author's response to reviews: see over
Dear Colleague,

Revision: MS: 1238374598614897. The association between delusional-like experiences, and tobacco, alcohol or cannabis use: a nationwide population-based survey.

Many thanks for the opportunity to revise and resubmit this article. We appreciate the reviewers thoughtful suggestions. We have revised the paper accordingly (changes shown in yellow highlight). The reviewers comments and out responses (in italics) and new text (indented) are shown below.

Please let me know if there is anything else we can do to assist with the review of this manuscript.

Yours faithfully,
John McGrath

Referee 1 (Dana March):

There are also several important limitations. First, and most importantly, the ANSMHW is a cross-sectional assessment, and no solid conclusions can be drawn about causality because temporality cannot be established.

We appreciate this limitation and have added more text to the discussion to draw the reader to this feature.

The study had several limitations. Importantly, the study was cross-sectional and it was not possible to establish the direction of causality between DLEs and the measures of substance use (we do not have information on the age-of-onset of the DLE). Using a prospective birth cohort and a nested sibling-pair study, we have previously reported an association between early cannabis use and later DLE and hallucinations [4]. We hope to explore the association between early alcohol and tobacco use and psychosis-related outcomes in this prospective cohort in future studies.

Second, lifetime disorders were assessed, and there is a literature indicating that lifetime diagnoses are more problematic than 12-month diagnoses. Why limit to lifetime diagnoses? If 12-month diagnoses are available, it might be worth presenting those data. If not, address this issue in the limitations section.

We do have data on twelve month substance disorders, but chose not to include this because the DLE items were lifetime ever (thus we could not restrict both the exposure and outcome measure to past year). However, past-year diagnoses are certainly more reliable and are worth looking at. We found that these analyses did not change the overall pattern of findings. We have included additional text.
Finally, we undertook several post-hoc analyses in order to explore the robustness of the findings. We examined the relationship between the variables of interest when the harmful use and dependence disorders for both cannabis and alcohol were restricted to past year diagnoses (instead of lifetime ever). The pattern of findings remained unchanged (data not shown). We also examined the association between alcohol use disorders versus DLE when demographic variables such as migrant status, employment status and educational status were removed from Model 2. Again, the pattern of findings remained essentially unchanged (data not shown).

Second, there are some concerns about the potential for excessive statistical control. Table 1 should present descriptive demographic characteristics of the sample—who comprises the sample? This would actually be helpful in determining whether the wide range of correlated confounders for which the authors controlled in Model 2 of Tables 2-4 might actually induce bias via excessive statistical control. For example, migrant status, education, and income would be, presumably, quite related. It is possible that controlling for all 3 may be unnecessary. This becomes more of an issue with the inconsistent results in the alcohol section. You would not necessarily expect tobacco, alcohol, and cannabis use to vary so greatly in migrants, depending on the countries of origin. This issue merits more consideration, and the authors should address thoughtfully these points.

This is a good point and it is always a challenge to know how much or how little to adjust these models. Our ‘house style’ is to show a base model (age and sex), and then a more detailed model with a range of potential confounds. We ran the models again in order to explore potential suppression effects and other unforeseen consequences of overly-specified models. However, the results were stubbornly persistent. We have included new text to describe these post-hoc analyses (see above).

Third, the discussion section needs work. In Discussion>The association between DLE and tobacco use on pp.13-14, this section requires attention. The first sentence needs rewriting, and the two alternatives regarding the observed pattern should be framed as two potential explanations and developed further. Moreover, the inconsistent pattern of findings with respect to alcohol use and use disorders merits more than one sentence in the discussion section. Why were they inconsistent? This is unbalanced, given the information provided on tobacco and cannabis use. The authors need to place these findings in context.

Sorry – in retrospect this was glossed over. We have rewritten this text and adjusted the abstract and discussion to draw more to the alcohol findings.

For example, alcohol dependence was significantly associated with endorsement of screen items, but not probe items. The lack of association with the probe items may reflect lack of power, as these items were less frequently endorsed. There was some evidence that early onset of alcohol
use and dependence disorders were associated with DLE endorsement (most noticeably for probe items). While those with comorbid schizophrenia and alcohol use disorders have worse clinical outcomes [43], alcohol use has not been identified as a risk factor for psychosis. It is feasible that alcohol use may contribute to an abnormal persistence of DLE (i.e. while DLE endorsement usually decreases over age, those who use alcohol may have persistent DLE). This research question may be suitable for further scrutiny within longitudinal prospective studies.

Fourth, the limitations section also needs work. The sentence on p. 15, “While the analyses related to cessation of use in the previous use may help reduce the influence…” does not make sense. Please resolve and revise this part of the limitations section.

*Apologies for this clumsy sentence. It has been rewritten (see above).*

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Referee 2 (Ian Kelleher).

I have no major recommendations for changes but one minor point that the authors might like to consider is the possibility for interactions in their data. For example, we and others have previously shown that cannabis use interacts with other variables to predict psychotic experiences.(1, 2) Would it be possible to look at interactions between cannabis, tobacco and alcohol by stratifying to show the risk of DLEs in individuals across 4 levels of use (i.e., individuals who do not use any of the three substances, individuals who use 1 substance, individuals who use 2 substances and individuals who use all 3 substances)? This is not at all essential, just a suggestion (i.e., a discretionary revision).

*We do plan to explore the issues of dose-response (one versus more types of substances) and interactions between different substance use disorders versus general mental health outcomes. However, we plan to examine this question within the context of a wider range of risk factors for DLE. In particular, we are examine the links between trauma exposure (esp. Childhood abuse) plus one or more types of substance use versus DLE as the outcome. We have previously found robust links between trauma exposure and DLE in this cohort. We feel that these second-order questions would be best addressed in a stand-alone paper.*