Author's response to reviews

Title: Lifestyle factors, demographics and medications associated with depression risk in an international sample of people with multiple sclerosis

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Author's response to reviews: see over
Dear Dr O’Neil

Re: Manuscript 6871346891381394 - Lifestyle factors demographics and medications associated with depression risk in an international sample of people with multiple sclerosis

Thank you for your careful review of our paper ‘Lifestyle factors demographics and medications associated with depression risk in an international sample of people with multiple sclerosis’ which we submitted for consideration of publication in your journal. Your reviewers raise some interesting and important points which we agree will make the paper stronger. We have revised the paper in line with these comments. We respond to the comments below individually, with each comment listed first, our response in italics, and the exact change we have made in the revised paper in bold. The changes in the revised paper are tracked so that they can be checked.

Reviewer: Jerome Sarris

Abstract

*Be specific about what type of study this is in the abstract- a cross sectional analysis?

We have made this change as follows: **This cross-sectional analysis recruited a total of 2459 participants via Web 2.0 platforms.**

* Spell patient health questionnaire. We have made this change as follows: **using the Patient Health Questionnaire-2 (PHQ-2).**

* Advised to clarify what "screened positive for depression on PHQ-2. I can’t imagine there is a definitive diagnostic element to this. We have made this change as follows: **…screened positive for depression (PHQ-2 score \( \geq 3 \)).**

* I would consider adding limitation in there somewhere e.g. cross sectional data and not longitudinal (also in methods and discussion/limitations. We have made these changes as follows: Abstract Conclusion: the following sentence added: **Planned longitudinal follow up may clarify causality.** Similarly we have added this sentence to the paragraph on reverse causality in the Limitations: **Planned longitudinal follow up of participants may help clarify causality.**

Methods

*I would like to see more detail on the depression questions for the PHQ-2. Especially considering this is the key outcome for your paper. We have added in Box 1 which outlines the exact questions and scoring for the PHQ-2
* How was this 'advertised' and did they receive any compensation for participation? We have added in a few words as follows to the first paragraph of the Methods to clarify this: In summary, participants were recruited via posting a link to the survey on Web 2.0 platforms that engaged people with MS. There was no compensation for participation.

* Trial registration number? As this is not considered a clinical trial under the guidelines for trial registration, it has not been registered.

Discussion

* Have you considered if people from North and South hemispheres may have different mood levels due to seasonal difference when completing the interview? Could be a confounder... The effect or otherwise of latitude on mental health outcomes will be analysed in a future paper from this dataset on latitude, sun exposure and vitamin D associations.

* Table - I would had in the footnote what the positive screen for depression actually means. We have added the footnote (to Table 2 and 3 in fact) as follows: ^ PHQ-2 score ≥3

* It is good you have highlighted the anti-inflammation nexus with MS and depression. I would emphasis this a little more, and can also find data on exercise, meditation, and smoking re reduced inflammatory biomarkers. We have emphasized this, adding the following to this section: Several of the lifestyle behaviours found to be associated with depression risk in our study have also been shown to modulate inflammation, such as smoking, exercise and meditation[50-52].

Discretionary Revisions

* I would seriously consider making some simple bar chat figures for your very interesting data. Esp the omega 3 and diet data showing that dose-dependant effect...

  Thank you for this suggestion, we have now added bar charts.

* Response options categorised for the purpose of analysis for meditation- as ‘never’, ‘less than once per week’ or ‘once or more per week’. This appears to be dichotomous e.g. never or over one time per week. For future studies I would at least have a 2-4 times per week option. We have now re-analyzed these data with 4 categories (never, less than once a week, 1-4 times a week and 5 or more times a week) and have included these results in the manuscript.

Reviewer: Anne Kavanagh

My main problem is that I believe there is a risk of substantial reverse causation which they argue in the discussion is unlikely to be large. We have removed our argument from the Limitations that reverse causation is unlikely to have a large effect, instead saying: Reverse causality may contribute to these associations as depression may result in less healthy behaviours, such as being sedentary, eating badly, and smoking, perhaps through low motivation.

Major compulsory revisions:

1. Please modify discussion to reflect my concerns with respect to reverse causation outlined above. We have modified the Limitations in line with this as noted above, and changed the wording where we have implied causation, as follows in the last paragraph
of the Results: Meditation was associated with lower odds of screening positive for depression, …In the paragraph in the Discussion about exercise, we have modified the text where it implies causation to: Participants with high levels of exercise had half the odds of screening positive for depression …

2. As all the data is self-report there misclassification (measurement error) is likely. It is also likely that this error is correlated between the exposures and outcomes due to some unmeasured variable such as personality type resulting spurious associations. Please discuss the possibility of measurement error due to self-report and the potential for this to be correlated between the exposures and outcomes (dependent misclassification) thus biasing results. The degree to which this is a problem is not known.

Did the authors test the association between doctor diagnosed depression and PHQ2 in this sample? If this is strong this provides some evidence that the findings are robust. We thank the reviewer for this insightful observation. We are unable to verify actual doctor diagnosed depression due to the size and international nature of the study. We have addressed this in the Limitations as follows: Participants self-reported data so the potential for recall bias exists, as well as measurement error, and the potential for this error to be correlated between the exposures and outcomes (dependent misclassification) thus biasing results. The degree to which this is a problem in our data is not known.

3. Is it possible to test for more categories in the meditation analysis - once a week is still infrequent? It would be interesting to see if more frequent meditation had a stronger association. We have now re-analyzed these data with 4 categories (never, less than once a week, 1-4 times a week and 5 or more times a week) and have included these results in the manuscript.

4. Throughout the manuscript the authors say “x times the risk” when the estimates on the odds ratio scale. At the start of the results paragraph on demographic risk factors and depression they do present results on the odds ratio scale however later in the paragraph and elsewhere in the manuscript they revert to using language which implies they are estimating the relative risk. (e.g. Participants who were separated or divorced had 1.7 times greater depression risk than those married or co-habiting.) We have modified ‘depression risk’ to ‘odds of screening positive for depression’ where applicable throughout the manuscript.

5. I think marital status should be included in the model as a potential confounder and suggest they collapse the categories and include it. We collapsed this variable down into three categories and entered it into the model. Table 1, 2 and 3 and corresponding text has been amended.

6. I suggest they delete the sentence on why they did not present analyses separately by gender. The fact that there are no differences in prevalence of depression is not the issue. Stratification is only needed if they believe that there is effect modification (where the lifestyle/depression associations differ by gender). We have deleted this sentence as suggested.

7. Please include 95% confidence intervals on the odds ratios in Table 2. This has now been included and the odd ratios have been amended to show 2 decimals as consistent with table 3.

8. Spell out SPQ when first used. This has been done.
9. Under the section on data analysis the authors say “due to variation in item completion, analyses were calculated using item response as the denominator”. I do not understand what they mean by this? Do they mean missing variables or items on a scale (e.g. PHQ2)? This actually refers to missing variables as per point 10 below. We have modified the statement to make it clearer as follows: The denominator for each item varied due to variation in the number of participants completing each item, as per tabulated results.

10. Could the authors please provide information on the extent of missing information on all the variables? These can be calculated from the denominators reported in the tables, as per item 9 above. Also how many people did not complete all items on the scales and what did they do about this. Are there standard procedures for dealing with missingness on the PHQ2? We only included participants who completed both items on the PHQ-2 in accordance with scoring instructions, and sufficient items on the other scales (DHQ and IPAQ) to calculate a score as per scoring instructions.

We hope we have attended to the reviewers’ comments satisfactorily, and that this paper can now be published in the journal.

Many thanks for your consideration.

Yours sincerely,

Dr Keryn Taylor
Corresponding author