Author’s response to reviews

Title: Excess Risk of Chronic Physical Conditions Associated with Depression and Anxiety

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Author’s response to reviews: see over
Dear Dr. Kemp,

I would like to thank you and the reviewers for providing us with valuable comments on our manuscript entitled “Excess Risk of Chronic Physical Conditions Associated with Depression and Anxiety” (manuscript # 1280381089988595). We have addressed all the reviewer comments and made changes accordingly in our revised manuscript. Please see our detailed responses to reviewer comments in the following section. The revised manuscript is attached with this submission. Please let me know if you need any other document from my side.

We look forward to your decision.

Thank you,

Sincerely,

Rituparna Bhattacharya
We thank the referees and the editor for their helpful reviews. The comments of the reviewers are displayed in Italics text. We have highlighted the changes we have made in the original manuscript. We also provide responses to each of the points raised by the reviewers. The changes made in the manuscript are also summarized.

**Reviewer#1**

Thank you for addressing all of my comments. The manuscript is substantially improved and represents a nice contribution to the literature on the associations of depression/anxiety and chronic physical health conditions.

We thank the reviewer for appreciating our work on the manuscript.

**Reviewer #2**

The decision to exclude underweight participants due to the small sample size is a much more sound argument than excluding them because they may be “sicker” than normal weight participants. As mentioned in the previous reviews, obese adults are also more likely to suffer from chronic health conditions compared to their normal weight counterparts (which the authors also found with their data as described in the manuscript “obesity was associated with higher risk for all chronic physical conditions except for osteoporosis”). However, obese individuals are not excluded from the analysis. I imagine if the authors looked at the percent of obese participants who reported fair/poor self-perceived physical health, that this percentage would also be higher than the 7.7% reported for normal weight participants. Delete any reference to excluding underweight participants due to their self-reported health; use the rationale of small sample size prohibiting comparisons as your justification for omitting this subset of participants.

As suggested by the reviewer, we have only used small sample size as the rationale for excluding underweight individuals.

In my previous review, I inquired about why the authors discussed the relationship between chronic health conditions and lifestyle factors in the results and discussion when these analyses were not hypothesized or described as aims. I did not question why these variables were controlled for in the depression and anxiety analyses. The only aim of the study is to “examine excess risk of a diverse set of chronic physical conditions associated with depression and/or anxiety in a non-elderly adult population within a multivariate framework that controlled for demographic and modifiable lifestyle risk factors.” It is unclear why the association between lifestyle factors and chronic health conditions is examined for the results and commented on in the discussion. Are these findings intended to help the reader understand the depression and anxiety results? These sections should either be deleted from the manuscript or justified.

As suggested by the reviewer we have now deleted sections reporting and discussing associations between lifestyle factors and chronic health conditions. However, in the penultimate section of discussion section (Page 15) we discuss the high rates of poor physical health, obesity and smoking among those with depression and/or anxiety as apparent from Table 1. We think it
is important to point this out in order to have better management of depression and/or anxiety in primary care and also better management of chronic diseases in mental health care.

Despite their assurances that the authors removed references to “psychiatric disorders,” there are still some instances in the manuscript (e.g., page 15, “with or without psychiatric disorders”).

We apologize for the omission and we have made sure that the term “psychiatric disorders” has not been used in the revised manuscript.

**Reviewer #3**

I appreciate the authors trying to show co-linearity between psychotropic use and having anxiety/depression, however this reviewer still has a major concern about the validity of the final results. Despite the statistical reasoning, there is a compelling evidence linking psychotropics with many physical conditions. One can just read any of the psychotropic drug monographs and can see the multitude of potential side effects. If the authors are concerned about co-linearity between medications and psychiatric conditions, how about the co-linearity between smoking and respiratory diseases, smoking and cardiovascular diseases, BMI and diabetes, BMI and age, etc...

Having 7 dependent variables should be adjusted for multiple testing using Bonferroni (0.05/7 = 0.007 should be the minimum acceptable significance level). Exact p values should be provided in the tables and throughout the results section.

We now consider findings significant only when p-values are less than or equal to 0.007. However, as suggested by the reviewer, we have provided the actual p-values in the table unless they are <0.0001.

We agree with the reviewer that there is evidence linking psychotropic medications with development of many chronic physical conditions. However, we are concerned that less than 1% of individuals (0.6%) with comorbid depression and anxiety did not use psychotropic medications. In terms of unweighted numbers, among those with osteoporosis only 3 adults with comorbid depression and anxiety did not use psychotropic medications. Similarly among those with diabetes, only 15 individuals with comorbid depression and anxiety did not use psychotropic medications. Similarly, the numbers were very small for heart disease (n = 21).

The reviewer is correct in noting collinearity between smoking and respiratory diseases, smoking and cardiovascular diseases, BMI and diabetes. However, in our models respiratory diseases, cardiovascular diseases and diabetes are considered in the context of associations between dependent and independent variables. Therefore, the relationship between BMI and diabetes, smoking and cardiovascular diseases are not considered within a multi-collinearity perspective (Wooldridge, Jeffrey M. Introductory econometrics: a modern approach. Cengage Learning, 2012)

To address the concern of the reviewer, we additionally included psychotropic medication use in the regression models. In these regressions, use of psychotropic medications was independently
associated with increased risk of arthritis (ARR: 1.28; 95% CI: 1.15-1.42; P<0.0001), diabetes (ARR: 1.51; 95% CI: 1.27-1.78; P<0.0001) and hypertension (ARR: 1.23; 95% CI: 1.13-1.42; P<0.0001).

We also present adjusted Risk Ratios (ARR) and 95% Confidence Interval (CI) of depression-anxiety status from complementary log-log regression models so that they can be compared with original findings. As seen below, depression-anxiety status is associated with higher risk of chronic conditions except for diabetes; for osteoporosis the association with comorbid depression and anxiety group was no longer significant after controlling for psychotropic medication use. We urge extreme caution in interpreting these results, because of the very high correlation between psychotropic medication use and depression anxiety status variable (> 0.66).

We have revised our manuscript to include these findings and also note our concern about the high correlation between psychotropic medication use and depression-anxiety status variable. Please refer to “Secondary Analysis” subsection, under Results section on page 12.

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Depression Only</th>
<th>Anxiety Only</th>
<th>Comorbid Depression and Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARR [ 95% CI]</td>
<td>P-value</td>
<td>ARR [ 95% CI]</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.64 [1.45,1.85]</td>
<td>&lt;0.0001</td>
<td>1.54 [1.37,1.72]</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.74 [1.38,2.20]</td>
<td>&lt;0.0001</td>
<td>1.38 [1.08,1.77]</td>
</tr>
<tr>
<td>COPD</td>
<td>1.66 [1.39,1.99]</td>
<td>&lt;0.0001</td>
<td>1.56 [1.29,1.87]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.20 [0.99,1.45]</td>
<td>0.062</td>
<td>1.01 [0.81,1.25]</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>1.34 [1.08,1.66]</td>
<td>0.007</td>
<td>1.61 [1.30,1.98]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.27 [1.13,1.44]</td>
<td>&lt;0.0001</td>
<td>1.34 [1.17,1.53]</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.80 [1.10,2.96]</td>
<td>0.019</td>
<td>1.61 [0.98,2.65]</td>
</tr>
</tbody>
</table>

Note: Analytic sample comprises of adults, 22-64 years of age with no self-reported schizophrenia, psychoses, attention deficit hyper activity disorders, adjustment disorders, substance abuse disorders and personality disorders.

* Model controlled for lifestyle risk factors (body mass index categories, physical activity, smoking status), age, gender, race, education, whether residing in a metro area (yes/no), health insurance and any psychotropic medication use. Asterisks denote significant group differences compared to the reference group “No depression and anxiety.”

COPD: Chronic Obstructive Pulmonary Disease