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 and editor 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 and the editor. As the comment about psychotropic medication use was made by multiple reviewers, we have grouped the comments. The changes made in the manuscript are also summarized.

**Editor:**
Please specifically analyze the role of psychotropic medication use on outcomes in the revised version of the manuscript as recommended by 2 of the reviewers.

**Reviewer#1:**
The authors discuss the possible role of psychotropic medication in the observed associations between anxiety/depression and chronic health conditions. In their Response to Reviewers and limitations section, they note that they did not consider psychotropic medication use in their analyses given the possibility of multicollinearity. In the absence of evidence to support this statement, this reviewer is not convinced that multicollinearity poses a substantial problem given that many individuals with depression or anxiety do not take medications for these conditions and many of the those who use these medications may not qualify for a diagnosis of depression/anxiety given that their symptoms are controlled. As such, the authors should at least report the association between their four-category anxiety/depression primary variable and data on the use of various psychotropics to which they may have access. If multicollinearity is not substantial (e.g., a correlation of < 0.6), the authors should consider controlling for medication use.

**Reviewer#3:**
Despite the revisions made, I believe there are still unanswered questions including the use of psychotropic medications. The authors stated co linearity as a reason for not including medications in the model, however leaving out a major explanatory factor such as psychotropic medications when one tries to make an association between depression, anxiety and medical conditions is a major flaw. Besides, the authors are not accurate in stating that the majority of individuals with self-reported depression, anxiety are receiving treatment. Evidence from literature argues otherwise.

In the original version of the manuscript we did not include psychotropic medications use because of the high correlation between depression-anxiety status variable and psychotropic medication use. Any psychotropic medication use was identified from prescription for psychotherapeutic agents identified from prescribed medication file of MEPS using multum therapeutic class codes (code: 242).

As suggested by the reviewer, we had examined the correlation between depression-anxiety status and psychotropic medication use. The estimated correlation between the two variables was 0.66479.

In addition, we examined the unadjusted relationship between depression-anxiety status variable and psychotropic medication use with chi-square test. The results are summarized in Table below. As seen from the table, among adults with no depression and no anxiety only 2.5% reported using psychotropic medications. However, among those with comorbid depression and anxiety, 80.2% used psychotropic medications. Chi-square value for this relationship was 9,157.79.
Description of Psychotropic Medication Use by Depression-Anxiety Status
Medical Expenditure Panel Survey, 2007-2009 (Column %)
Chi-square = 9,157.79

<table>
<thead>
<tr>
<th>Depression Only</th>
<th>Anxiety Only</th>
<th>Comorbid Depression and Anxiety</th>
<th>No Depression and No Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Wt%</td>
<td>N</td>
<td>Wt%</td>
</tr>
<tr>
<td>ALL</td>
<td>2,326</td>
<td>100.0</td>
<td>1,719</td>
</tr>
</tbody>
</table>

Psychotropic Medication Use

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>Wt%</th>
<th>No</th>
<th>Wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression Only</td>
<td>1,496</td>
<td>66.5</td>
<td>830</td>
<td>33.5</td>
</tr>
<tr>
<td>Anxiety Only</td>
<td>657</td>
<td>40.7</td>
<td>1,062</td>
<td>59.3</td>
</tr>
<tr>
<td>Comorbid Depression and Anxiety</td>
<td>669</td>
<td>80.2</td>
<td>180</td>
<td>19.8</td>
</tr>
<tr>
<td>No Depression and No Anxiety</td>
<td>636</td>
<td>2.5</td>
<td>27,712</td>
<td>97.5</td>
</tr>
</tbody>
</table>

Note: Study sample comprised of adults aged 22-64 years alive during the calendar year without self-reported schizophrenia, psychoses, attention deficit hyper activity disorders, adjustment disorders, substance abuse disorders and personality disorders. Asterisks represent significant group difference in depression-anxiety status based on chi-square tests.

Wt: Weighted.

*** p < 0.001

We also examined the relationship with unadjusted logistic regression in which psychotropic medication use was the dependent variable and depression-anxiety status was the independent variable. The odds ratio estimates for use of psychotropic medication use and those with both depression and anxiety was 157.229 (95% CI = 126.75, 195.03) compared to those without depression and without anxiety. Odds ratio estimates for other categories (depression no anxiety, no depression and anxiety) were 76.95 and 26.64 respectively.

We now add text in method section as to why we did not adjust for psychotropic medications use in the regression models. Please see page 16.

Reviewer #1

The following sentence on page 6 of the Introduction section requires clarification: "We were specifically interested in examining whether depression and/or anxiety was independently associated with these seven chronic conditions, given that the lifestyle risk factors have been known to increase the risk for these chronic conditions [35]."

As life-style risk factors such as obesity have been reported to increase the risk of chronic conditions, we examined the independent association of depression-anxiety status on risk of having chronic conditions after controlling for obesity, smoking and lack of physical activity. Life-style risk factors are reported to be independently associated with the risk of the chronic
conditions examined in this manuscript. Therefore, if we control for these risk factors in our statistical model and still find a significant association between depression-anxiety status and chronic conditions we can estimate the independent association of depression-anxiety status and risk of chronic conditions. However, we have removed this sentence from our revised manuscript.

The authors should please provide the reference for the following statement on page 8 of their Methods: “The cross-walk file between ICD-9 CM codes and clinical classification codes are published.”

We now provide the suggested reference.

The authors should report exact p-values between 0.01 and 0.05 as well as test statistics given that these data may be essential to subsequent meta-analyses and other systematic reviews.

We now provide exact values if 0.01≤p<0.05 as footnote in the tables.

The authors’ response to reviewers indicates that they tempered their recommendation regarding the need for routine screening for common mental health disorders. Their statement about routine screening on page 14 is still quite strong, does not follow directly from their data, and requires further consideration. Routine screening may have a number of limitations if coordinated care is not implemented first and/or if their mental health providers are not available to follow-up with patients who screen positive. The authors’ language regarding this recommendation thus requires further revision or consideration of these limitations.

We have revised our language in the revised manuscript. We now add text regarding the importance of implementing co-ordinated mental-healthcare care alongside routine screening for depression and/or anxiety. Please see page 15.

On page 15, the authors identify “recall-bias” as a limitation of their self-reported data. It may be more appropriate for the authors to acknowledge “reporting bias” more generally as a limitation, given that recall bias is only one form of reporting bias.

We have done so. Please see page 16.

Reviewer #2

Given that depression and anxiety was self-reported and in response to questions about “mental or emotional health conditions, such as feeling sad, blue, or anxious about something,” the authors should refrain from discussing their results in the context of “common psychiatric disorders such as depression and/or anxiety” (p.12). Feeling anxious about something should not be equated with anxiety disorders such as obsessive-compulsive disorder, panic disorder...Please be more conservative with your language and refrain from any discussion of your variables as “psychiatric disorders” or “common mental health disorders”.

As suggested by the reviewer, we have refrained from referring to depression and anxiety as common psychiatric disorders in the revised version.
The authors need to cite their evidence for their rationale to exclude underweight non-elderly adults. As stated in their revision: “We did not include underweight individuals as they are often found to be sicker than normal weight counterparts.” Obesity is associated with greater risk of chronic disease and they are not excluding obese adults. Their response to this critique from the first submission is not clear, nor supported, unlike their other responses. Moreover, “found to be sicker” is vague, which makes it challenging to discern what types of illnesses the authors are concerned about confounding results in underweight individuals. If it is cancer that they are concerned about, why not exclude participants with cancer? Obesity is a well-documented risk factor for certain cancers (e.g., pancreatic, colon, kidney, and breast).

In our study sample, only 1.2% of adults were in the underweight BMI group. Among adults with underweight, almost twice as many individuals (15.2%) as those with normal weight (7.7%) reported fair/poor self-perceived physical health. In terms of depression/anxiety variable, in the underweight group, only 9 individuals reported having comorbid depression and anxiety, a cell size too small to analyze. Therefore, we excluded underweight individuals from our study sample.

Furthermore, we focus on the non-elderly adult population because individuals with depression and/or anxiety have been found to develop chronic physical conditions at an earlier age as compared to general population (Katon, 2011).


The cross-sectional nature of the data prevents the authors from concluding that depression/anxiety causes chronic illness, yet the discussion focuses exclusively on this potential pathway. Strong evidence exists for a bidirectional relationship between depression and type 2 diabetes.

We agree with the reviewer that the cross-sectional nature of the association explored in this paper does not allow us to comment on causality. We now point out the possible biological, pharmacological as well as access to care pathways that may explain the increased risk of chronic physical conditions associated with depression and/or anxiety.

We now acknowledge the bidirectional relationships between depression and chronic physical conditions such as diabetes. We have added text referring to this bidirectional relationship in our manuscript. Please see page 12.

In general, the discussion is quite superficial. The biological and pharmacological mechanisms exclusively focus on cardiac disease. What about the potential biological and pharmacological mechanisms associated with other chronic illnesses?

We now outline the possible biologic and pathogenic pathways of other chronic illnesses such as COPD, asthma, arthritis and osteoporosis. Please see pages 13-14.
The manuscript now focuses on the relationship between depression/anxiety and 7 different chronic diseases, after controlling for a number of variables. However, the results and the discussion discuss the findings related to the lifestyle factors and chronic disease. Why focus on these particular variables? They are not a part of the hypotheses/study aims.

We adjusted for a wide range of socio-demographic as well as life-style risk factors in our model. However, we are specifically interested in the association of depression-anxiety status with the chronic diseases after controlling for life-style risk factors like obesity, lack of physical activity and smoking, as these are known risk-factors for the chronic diseases included in the current study.

To address the concern of the reviewer, we also present and discuss the association between life-style risk factors and risk of chronic diseases in our results and discussion section. Please see pages 11-12 and page 15.