Author's response to reviews

Title: Pain, not chronic disease, is associated with the recurrence of depressive and anxiety disorders

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Author's response to reviews: see over
Dear Alice Murray,

Thank you for the interest you have expressed in our manuscript entitled ‘Pain, not chronic disease, is associated with the recurrence of depressive and anxiety disorders’. We are pleased that you have invited us to respond.

We would also like to thank the reviewers for their detailed and constructive comments on our manuscript. We have addressed the issues that the reviewers raised. We agree with virtually all suggestions and have revised the manuscript accordingly. Please find a point-by-point response to the reviewers’ comments in the text below, together with a detailed account of the changes. We hope that you find our updated manuscript acceptable for publication in its present form.

We look forward to your decision.

On behalf of the co-authors,

Yours sincerely,

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Reviewer: Weng Yee Chin

This is an interesting analysis of a large, 4-year longitudinal cohort study on subjects derived from the general Dutch population, primary care, and various mental health providers. The investigators should be commended on the follow-up duration of the cohort, as there are very few longitudinal studies which are long enough to be able to examine the factors affecting relapse.

- Major Compulsory Revisions
  None

- Minor Essential Revisions
  1. Although the association between the presence of chronic pain and relapse of depression is clearly identified, it is not clear whether the findings show that the sub-threshold depression is mediating the chronic pain or if the chronic pain mediates the depression relapse. The concepts may be easier to comprehend if there was a diagrammatic representation on the associations between pain and relapse found in the analysis.

    Re: In our article subthreshold depressive symptoms mediate the association between pain and depression relapse. We agree with the reviewer that a diagrammatic representation would contribute to the clarity of the concepts. Therefore in the Methods section we have incorporated the following model (page 8, line 23-28): “As shown in the model below, the results will show the effect “a” of the independent variable (pain variable) on the mediating variable (depression severity), and the effect “b” of the mediating variable on the dependent outcome (depression recurrence). The effect of the pain variables on the recurrence of a depressive disorder will be shown by the direct “c’” effect. The effect of the pain variables on the recurrence of a depressive disorder through depression severity will be shown by the indirect “a x b” and total “c” effect.”
2. I also wonder whether there is any effect of treatment and whether use of psychotropic medications or analgesics need to be controlled as potential confounders. A comment should be added about how the use of medication may or may not affect findings.

Re: We have additionally tested whether the use of psychotropic medications or analgesics were confounders of the associations. We have added to the Methods section (page 7, line 11-19): “Additionally, to account for possible psychoactive and pain medication effects, medication use was assessed based on drug container inspection of all drugs used in the month prior to the interview and classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. Antidepressants included selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (N06AA) and other antidepressants (N06AF/N06AX). Benzodiazepines included ATC-codes N03AE, N05BA, N05CD and N05CF. Pain medication included paracetamol (N02BE01), acetylsalicylic acid (N02BA), non-steroidal anti-inflammatory drugs (M01A, M01B), and opioids (N02A).”

In the Results section (page 10, line 8), we added our findings which did not indicate that medication use had any impact on the shown results. We added: “Additionally adjusting for use of psychotropic or pain medication did not alter any of the results.”

- Discretionary Revisions
Best to use ‘Chronic Pain Grade’ in Table 3 (instead of CPG)

Re: We have adjusted ‘CPG’ to ‘Chronic Pain Grade’ in Table 3.

Reviewer: Frank Jacobi

The present study examines the relation between chronic diseases, such as cardiometabolic or musculoskeletal diseases, pain characteristics and the recurrence of depressive and/or anxiety disorders in at baseline remitted patients for a 4-year follow-up period. In this study, only pain characteristics were associated with the recurrence of only depressive disorder. This association is mediated by subthreshold depressive symptoms at baseline. Data stem from a large study with sound design, analyses are adequate and the manuscript is well-written. However, in the following some remarks are listed that might improve the manuscript (all minor or discretionary revisions needed).

Method:
1. Please describe shortly how the censored recurrence time in months via Cox regression translate into the reported hazard ratios and specifically how to interpret the HR

   Re: Cox regression takes into account differences in time at risk for an event and censoring. Time at risk was measured from the moment the participant was assessed as being in remission until either the participant had an event, a recurrent depressive or anxiety disorder, or until the censoring moment of last follow-up, when the participant did not have a recurrence during the follow up period. Hazard ratios (HR) are the instantaneous chances to have a recurrence, and are comparable to relative risks. So during our 4-year follow-up, there was a significant association between pain and depression recurrence, for instance, neck pain was significantly associated with 45% increased risk for depression recurrence (HR 1.45, p=.005) and per grade increase on the Chronic Pain Grade participants had an 18% increased risk for depression recurrence (HR 1.18, p=.01). We have added this to the Results section (page 10, line 3-4).

2. Was any kind of power analyses conducted in advance, i.e. did the chronic diseases and pain have the same chance to show a significant association with
depression or anxiety recurrence (given that there is a true association)?

Re: Since we have used data from a large observational cohort study, we did not perform power analyses. We do acknowledge that certain chronic diseases had low prevalences therefore we analyzed disease categories rather than single diseases to reach reasonable numbers. We have added as a limitation in the Discussion section (page 13, line 19-20): “The prevalences of specific chronic diseases (myocardial infarction, epilepsy etc.) were quite low, so our capacity to study the role of all diseases individually was limited”.

Results:

3. Table 1: a) please provide a further column providing N in each row (where applicable) in order to get a better feeling of base rates and power (see above).

Re: We have now not only provided the percentages, but have added the corresponding N in Table 1.

b) Chronic pain grade: please do not provide the mean but rather % of the following groups: no pain, grade 1, grade 2, grade 3, grade 4

Re: We have added this information in Table 1.

4. To get a better feeling of the magnitude of the effects, please provide numbers for recurrence (anxiety, depression, both) in persons with vs. without any chronic disease, as well as with and without having a chronic pain grade >=2 vs. <2

Re: We have added to the Results section (page 9, line 8-14): “Of the participants, 424 (37.8%) experienced a recurrence of a depressive and/or anxiety disorder during the follow-up period. Of participants with at least one chronic disease 39.1% had a recurrence, whereas participants with severe or disabling pain (CPG>=2) 42.4% had a recurrence. When considering depression and anxiety recurrence separately, 26.0% and 22.7% participants had a recurrence, respectively. For depression recurrence, participants with severe or disabling pain (CPG>=2) were more likely to experience a recurrence; 30.9%”.

5. Table 3: a) since there is no variance in rows 2 (M) and 3 (DV) these can be
omitted and replaced by a notice in headline or footnote, b) What is the “Effect of X on Y” measure? What is the difference between direct and total effect (both labeled with “(c)”)? What is “ab”, i.e. which confidence interval is meant? (a table must explain itself)

Re: a) We have adapted Table 3.

b) In response to Reviewer # 1 (remark 1) we have added a model with explanatory text in the Methods section explaining the different steps (page 8, line 23-28): “As shown in the model below, the results will show the effect “a” of the independent variable (pain variable) on the mediating variable (depression severity), and the effect “b” of the mediating variable on the dependent outcome (depression recurrence). The effect of the pain variables on the recurrence of a depressive disorder will be shown by the direct “c’’ effect. The effect of the pain variables on the recurrence of a depressive disorder through depression severity will be shown by the indirect “a x b” and total “c” effect”.

Discussion

6. In particular with regard to practical implications (e.g. for GP) please describe in numbers or proportions a) what is the probability to have a relapse within next four years in patients with (CPG>=2) vs. without pain in persons with fully remitted anxiety/depression and b) the same in persons with remitted but still subthreshold anxiety/depression

Re: a) We have added to the Discussion section (page 11, line 2-3): “During follow-up a quarter of all participants had a depression recurrence, while a third of participants with severe or disabling pain had a recurrence”.

b) We have used a continuous measure for subthreshold depressive and anxiety symptoms, which does not allow us to provide proportions here. All patients did not have a disorder at the first assessment but many had some subthreshold symptoms.

7. See above: the discussion of the counter-intuitive Null-effect of chronic conditions should be supplemented by a statement whether this result might be an artifact or not (power)
Re: See our response to remark 2. We have added as a limitation in the Discussion section (page 13, line 19-20): “The prevalence of specific chronic diseases (myocardial infarction, epilepsy etc.) were quite low, so our capacity to study the role of all diseases individually was limited”.

8. Please discuss possible indications for differences within depressive and anxiety groups (e.g., potentially stronger in Dysthymia, or in panic disorder)?

Re: We agree with the reviewer that a more diagnostic detail would have been interesting. Participants were indeed diagnosed with specific depressive and anxiety disorders. It was, however, not our goal to examine the different effect of physical health on recurrence of specific disorders. Specific depression and anxiety diagnoses are also often co-morbid and lack stability over time (reference 1. Lamers et al. 2011; reference 2. Hendriks et al. 2013). Therefore, we chose not to analyze these distinctive categories of depressive and anxiety disorders. We have added to the Limitations section: “We analysed depressive and anxiety disorders separately but did not analyse differences between specific depressive or anxiety disorders” (page 13, line 22-23).

9. The present study adds (indirect) evidence for the hypothesis that depressive disorders should be treated until full remission (but of course cannot prove this because no treatment variables were taken into account) – please discuss this topic a little more in detail.

Re: We have extended the part about clinical implications in the Discussion section (page 13, line 2-3): “The current study suggests that it may be of benefit to prolong depression treatment until full remission, especially for those patients who also experience severe pain symptoms, as they are a risk group to remit into full-blown disorders”.

References: