Author’s response to reviews

Title: Symptoms of depression are associated with physical inactivity but not modified by gender or the presence of a cardiovascular disease; a cross-sectional study.

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Author’s response to reviews:

Concerns cover letter BMC cardiovascular.

Dear editor,

On behalf of the authors, we are grateful for the opportunity to submit a revised version of our manuscript ‘Symptoms of depression are associated with physical inactivity but not modified by gender or the presence of a cardiovascular disease; a cross-sectional study’. We appreciate the comments of the editor and reviewers, which increased the quality of the paper.

Below we describe point-by-point the response to the comments including additional analyses that were carried out, and a detailed reflection on the requested revisions. The changes to the manuscript are highlighted, except for the textual and grammatical adjustment that were made after editing by a native speaker. The questions about statistics have been answered together with a statistician.

Kind regards, on behalf of the authors,
Retze Achttien, MSc

Janey Peterson (Reviewer 1):

*       The paper requires editing in English language.

-       The comments of the reviewers were processed. Thereafter editing was performed by a native English-speaker.

*       Suggest authors use term "depression and depressive symptoms" as most of the literature in this area focuses on depressive symptomatology and not depression:

-       We agree and adjusted it. We now consistently use the term “symptoms of depression” throughout the manuscript. If we refer to literature that uses specific terminology, we choose to follow the authors and use the terms “depression, depressive symptomatology etc.”.

*       Line 100: We included baseline data from the RCT [28] consisting of primary and secondary prevention patients. This sentence is unclear and would benefit from adding a reference and more details.

-       We changed this sentence into “We included the baseline data from a RCT [29] that focussed on the effects of cardiovascular risk management for primary and secondary prevention patients.” Lines 107-109.

*       Line 103: what is a cardiovascular attack?

-       We apologize for this. This was indeed not correct. We changed it into the more specific term “Stroke”. Line 111.

*       Lines 105-7: These 2 sentences should start the paragraph. Poor language skills should be further operationalized.
We started the paragraph with the 2 sentences. “All patients were 18 years or older and were able to provide informed consent. Exclusion criteria were diabetes mellitus, pregnancy and lactation, terminal illness, cognitive impairment, and insufficient mastery of the Dutch language hindering reading and answering the questionnaires.” Lines 105-107.

Moreover, we changed the text “poor language skills” into “insufficient mastery of the Dutch language hindering reading and answering the questionnaires”. Lines 106-107.

* Line 120: Provide the details of the sample size and the study outcomes with references:

We carefully considered your comment but to our opinion the study outcomes of the RCT are not relevant for this study, because these outcome data are not used. We only included baseline data of this RCT. Relevant information of our study and sample size has been described in the sections “study design”, “setting” and “participants”. Lines 89-114. We did report the sample size that was used in our study. Line 100-101. …. and 2184 patients that were included in our study….

* Lines 155-6: was multicollinearity evaluated with the interaction terms? Auto correlation is for time series not a cross sectional study. Suggest reporting ICC

Yes, multicollinearity was evaluated with the interaction terms. The VIF factors were respectively 11.35 and 12.57 for the interaction terms Gender*PHQ-9 and primary/secondary prevention group*PHQ-9. This means that there is an indication that indeed multicollinearity may affect the estimates. On the other hand, the confidence intervals are still reasonably small. Further, it is important to realize that these terms add nothing to the explained variance. When all independent variables are included (Table 2, model 1), the explained variance is 0.081. The explained variance for Models 2 (primary/secondary prevention group*PHQ-9: B=0.01, 95%CI -0.02-0.05, p=0.47) and 3 (gender*PHQ-9: B=0.02, 95%CI -0.02-0.05, p=0.44) remain 0.081, so it can be concluded that these variables did not contribute to the explained variance. It should be noted that the explained variance for PHQ-9 alone is 0.020, so the other independent variables did not have added value to the explained variance. To our opinion, it is not relevant to report this in our manuscript.

We agree that auto correlation is not relevant in a multilevel analysis. We want to apologize for this, this was by mistake not removed from an earlier version of the manuscript. The term is removed. Line 165.

We calculated the ICC=0.017. We reported it in Line 212. “Assumptions for multilevel linear regression analyses were not violated and no effect for clustering was found (ICC=0.02).”
* Lines 161-2: Please clarify the interaction terms - were 2 separate interaction terms added for primary and secondary prevention?

- We added the interaction terms separately to the model (primary/secondary prevention group*PHQ-9 and gender*PHQ-9 respectively).

o We revised Table 2 to clarify this.

o In the text we adjusted the following sentences “……, by adding the interaction terms (primary/secondary prevention patients*PHQ-9 and gender*PHQ-9 respectively) to separate models”. Lines 172-173

o We adjusted the sentence “The association between symptoms of depression and physical inactivity was neither modified by the interaction term primary/secondary prevention group*PHQ-9 (p=0.55: Table 2, model 2) nor by the interaction term gender*PHQ-9 (p=0.44: Table 2, model 3). Lines 217-219.

* It would be helpful to have a consort table of the number screened, included/excluded and the reasons for the study:

- We carefully considered your comments, but to our opinion the presentation of the consort table, that was used in the RCT [29] to which we have referred, seems redundant. Relevant information for our study is described in Lines 100-101 “A random sample of 1600 general practices in seven geographical areas in the Netherlands was invited to participate in the RCT [29], resulting in a sample of 34 practices and 2184 patients that were included in our study.

* Please add p values to the comparisons in table 1:

- We prefer not to do this. Table 1 presents descriptive data of the study population. In our view adding p-values doesn’t contribute to answer the research questions.


- We added the non-significant interaction terms to the model separately. See table 2.

- For this issue we refer to our previous answer about multicollinearity.

- We performed the Hausman test and found a p value of 0.08. The test result supports the use of a random effects model instead of a fixed effects model.
* First, the study should emphasize that it is not possible to draw any causal relationship due to the design of the study

- We added the sentence “Due to the cross-sectional study design however, it is not possible to draw any causal relationship. This is an important limitation of this study design” to the discussion section. Line 250-252.

* Second, there are some very important variables, such as BMI, that were not described in the text and were not used to adjust the model. BMI, for example, is bidirectionally associated both with PA and depression. Please, take a look on potential correlates of PA and dep


We added to the discussion section “In particular the body mass index might have been a potential confounder, as it has been reported to be associated with lower activity levels in depressed patients [41].” Lines 245-246.

We added “and biological correlates (body mass index, physical co-morbidities)” to line 244.

We added to the discussion section “In addition, it was reported that adults with major depression disorders do have low levels of physical activity [41].” Lines 259-260. And added “It should be noted that our population predominantly had no (81.4% of the primary and 69.9% of the secondary prevention patients) or only minor symptoms of depression”. Line 264-265.

We were not able to use BMI in the analyses due to the large number of missings in our data. We only have the BMI for 130 female (missing: 68%) and 180 male (missing: 79%) in the primary prevention group, and respectively 68 female (missing: 81%) and 133 male (missing: 85%) patients in the secondary prevention group. We added to the discussion section (Lines 246-248): “We did not correct for the BMI variable in our model, due to the substantial number of missing data (77%). This is a limitation of our study.”

However, to give you some insight, we did run the analyses in the subgroup of patients with BMI data available (n=497). We checked and compared in this subgroup the regression coefficients in models with and without adjustment for BMI (please see_response_letter_BMC_after_revisions_including_BMI_models; attached as supplementary material). The association between depression and physical activity was consistent across the models with or without adjustment for BMI and no indication for confounding by BMI was found. Of course, the subgroup of patients whose BMI had been measured is different from the entire cohort and we should be cautious to interpret these results (subjects with BMI data available were significantly more active and less depressed than subjects without BMI data).

Minor

* The sentence on Page 3, Line 58 seems incomplete and it is not very clear to me... “Depression acts as a barrier to enhance physical activity and efforts to improve lifestyle [6-8].

* We changed this sentence into “Depressive symptoms may impede the successful stimulation of physical activity and patients’ efforts to improve lifestyle”. Lines 60-61

* P values are never = 0.00. Please change to P<0.01 or report the full value.
- We adjusted these P values throughout the text in the results section and in table 2.

* Please check for use of " , " throughout table 1.

- We have carefully checked for the use of “,” table 1. We have replaced all “,” for “. “

Incorrection found by ourselves:

* We found ourselves that we accidently reported the p value of Patient group (SP/ PP) in the text (Line 218) instead of the P value of the interaction term for primary/ secondary prevention group*PHQ-9. We replaced the p=0.55 for p=0.47.