Author’s response to reviews

Title: Depression and Anxiety as major determinants of neck pain: a cross-sectional study in general practice

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

We thank you and the reviewers for the many thoughtful comments offered regarding our manuscript MS 2042568431219709. Please find attached the revised manuscript, and a point to point response to the reviewer comments. Additionally, a native speaker revised our paper in order to improve the style of written English. We hope that we have been responsive to the concerns raised and thank you in advance for your additional consideration for publication of our manuscript in BMC Musculoskeletal Disorders. Please do not hesitate to contact us should there be any problems or questions.

Yours sincerely,

Martin Scherer

Manuscript resubmission
Original paper MS 2042568431219709
Title: "Depression and Anxiety as major determinants of neck pain: a cross-sectional study in general practice"
We have reviewed each comment carefully; our responses are directly beneath the original reviewer comment.

Reviewer 1: Scott Patten

Major Compulsory Revisions:
1. The study has both strengths and weaknesses. One issue that stands out immediately when one reads the abstract is a discordance between the stated aims and conclusions and the usually accepted limitations of the cross-sectional study designs. The background section of the abstract states that the aim is to determine who might benefit from psychosocial, as opposed to medicinal, therapies. This aim could not possibly be addressed using cross-sectional data from general practice, and in fact the study doesn’t evaluate the effectiveness of different interventions. The conclusions again refer to the efficiency of treatment, which cannot be assessed using this kind of study design.

   We fully agree with this important remark. We now clarify the aims and the conclusions of our study throughout the whole manuscript. See our changes as follows:

   **Abstract – background**
   “It aims to recommend selection criteria for further evaluation which might help to identify patients who might rather benefit from psycho-social interventions than from medicinal therapies.”

   **Abstract – conclusions**
   “The higher the neck pain level, the more attention should be paid to psychosocial distress as a related burden. Further research is needed to elucidate the causality and the direction of the association between psychosocial distress and neck pain and to determine the benefit of psychosocial interventions.”

   **Introduction (last paragraph)**
   “This study aims to identify socio-demographic, psychometric, medical history, and health-promoting lifestyle factors which might interfere with neck pain. In addition, and it aims to recommend selection criteria for further evaluation which might help to identify patients who might rather benefit from psycho-social interventions than from somatically based therapies.”

   **Conclusions**
   “The present study suggests that the degree of neck pain was gradually related to psychosocial distress and that different levels of neck pain might discriminate patients with different degrees of psychological distress. (...) Findings of this study underline the need for further research that determines whether neck pain therapies are more likely to be efficient if care for chronic patients is not only symptom-oriented but focuses on psychosocial factors.”

2. I have some questions about the measures employed in the study. The measure of depression and anxiety is fully appropriate, but the measure of neck pain is described as a measure of disability rather than being a measure of pain. This is an important distinction that needs to be more carefully addressed.
The NPAD is an instrument designed to measure neck pain and related disability and it includes an assessment of the degree to which cervical spine pain interferes with various activities of living and causes emotional distress. It is a measure that quantifies neck pain in its different dimensions, but does not specifically measure disability. To clarify this we rephrased the 4th paragraph of the Methods section. Additionally, we replaced Appendix 1 (NPAD-d) by the original English version of the instrument (NPAD) to facilitate insight in the design of the scale for the non-German speaking reader.

“The NPAD is a 20 item measure specifically developed for patients with neck pain to assess neck pain and related disability.”

Another issue involving measurement is the statement in discussion that inadequate physical activity was associated with neck pain. Elsewhere, it appears that “regular” physical activity was assessed.

We apologize for the misleading wording. We clarified by using consistent wording throughout tables and text:

**Methods:**

“Single item questions were used to ask ... for exercise frequency per week.”

**Whole manuscript:**

We replaced “inadequate physical activity” by “infrequent physical exercise”.

3. The argument that the sample is representative of the target population seems weak in view of the low response rate (about 1/3), and there is no discussion of the possibility that selection bias could be introduced as a result of the low response rate. The second paragraph in the discussion section highlights several potential limitations of the study, including the “temporality” issue due to the study design, but the stated limitations appear to have been ignored in the interpretations expressed elsewhere in the paper.

We removed the statement that the study is “representative for the typical chronic neck pain patients seen in primary care” and added this issue to the limitations of the discussion section:

“First, our study is limited by the somewhat large number of exclusions. However, our study was conducted in a relatively large group recruited by a defined algorithm from the whole patient population of various practices (Figure 1). The exclusions can be traced back to predefined reasons according to this algorithm, so it is unlikely that the sample was subject to an unintentional selection bias.”

**Discretionary Revisions:**

4. In my view, the main implications of the study are for further research. Since depression and anxiety are associated with neck pain (or neck pain disability?), it seems possible that depression and anxiety are causing neck pain, or contributing to its persistence and also that neck pain may increase the risk or decrease the prognosis of depression. Longitudinal studies will be needed to assist with these distinctions. To some extent, such issues are alluded to in the discussion, but this aspect of the paper should be expanded, I believe.

Again, we thank the reviewer for this important suggestion and extended the conclusions as follows (see also response to comment # 1):

“Findings of this study underline the need for further research that determines whether neck pain therapies are more likely to be efficient if care for chronic patients is not only symptom-oriented but focuses on psychosocial factors.”
5. Finally, I would reiterate that I think the final conclusions, that people with high levels of depression and anxiety would be better managed with psychosocial interventions cannot possibly be supported by the data presented. At least some rewording seems warranted, in my opinion.

We reworded the conclusions (please see also response to comment # 1).

6. I believe that the word "interact" would be a better choice than the word "interfere" in both instances where this word occurs in the paper.

We have done that.

Reviewer 2: Swenne van den Heuvel

Reviewer's report:
Major compulsory revisions
In general, the study deals with an interesting subject, the relationship between psychosocial factors and musculoskeletal symptoms, in the present case psychological distress and neck pain. However, the objectives of the study need some clarification, in particular the second objective (with regard to selection criteria). As it is formulated now, the methods of the study do not seem fit to answer them. Therefore, the conclusions of the article are premature and cannot be drawn on the basis of the results of this study. Furthermore, the writing needs improvement. Finally: it is interesting to hear follow-up surveys are under way. Longitudinal data might be more fit for some of the study objectives.

Major remarks:
1. The NPAD measures neck pain and limitations involved. Part of it refers to emotional factors. The authors write the NPAD supports constructs of mood and neuroticism. I wonder if an association between this scale and a scale measuring anxiety and depression is not too obvious.

We do not believe that the association between the NPAD and anxiety and depression is too obvious. The NPAD asks whether neck pain interferes with emotions but does not include questions about depression symptoms or signs for anxiety. To make this more evident for the non-German-speaking reader we replaced Appendix 1 (NPAD-d) by the original English version of the instrument (NPAD).

2. In the study two objectives are mentioned: (1) to identify socio-demographic, psychometric, medical history, and health-promoting lifestyle factors which might interfere with neck pain, and (2) to provide selection criteria for patients who might rather benefit from psycho-social interventions than from medicinal therapies. A peculiarity of the structure of the article is that the background part is written more or less like an introduction to the second objective, while the analyses described in the article are aimed at the first objective. It is
unclear how the study results could contribute to the provision of selection criteria, as mentioned in the second objective. It is clear that a high pain score on the NPAD is associated with depression and anxiety. Apart from that this might be caused by the fact that the NPAD measures a certain degree of psychosocial distress itself (see previous point), it is not clear if the neck pain is caused by psychosocial distress or the other way round. It is certainly not clear what intervention is the most proper in subjects with this combination of a high NPAD score and high psychosocial distress. For that purpose a RCT design is needed. The conclusion that general practitioners should use instruments to measure depression and anxiety, in order to identify patients in need of a psychosocial intervention is totally unfounded. The study results produced no results referring to causes of the symptoms, nor to effectiveness of treatments or interventions.

We agree with this objection and apologize for the imprecise wording. We rephrased the relevant parts of our manuscript (please see response to comment #1 of Reviewer 1).

3. The authors state that the study population is likely to be representative for the typical chronic neck pain patients seen in primary care. However, the non-response was very high and I don’t see results of a non-response analysis in the article.

We removed the statement that the study is “representative for the typical chronic neck pain patients seen in primary care” and added this issue to the limitations of the discussion section (please see also comment #3 of Reviewer 1).

4. The relation between neck pain (or broader musculoskeletal pain) and psychosocial distress has been examined before. I miss a comparison with previous literature.

We expanded the Discussion section, compared our results with what is known from previous research and discuss the contribution of our study: “In fact, results from this study are coherent with what is known from previous research. A recent systematic review investigated determinants and risk factors for neck pain in the general population and found consistent evidence only for psychological health factors and for other health problems like musculoskeletal complaints and poorer self-rated health. [18] This indicates that high-level evidence was reproduced by this study, and that results derived in a general practice setting using practical self-administered instruments are very likely to be valid.”

5. I assume physical factors, such as work-related exposure, are not included in the questionnaire. Consequences should be considered in the discussion, and not only the remark that the lack of these factors is a limitation.

We expanded the corresponding section in the Discussion to emphasise the significance of working conditions for assessment and management of neck pain in workers: “Physical job-demand characteristics and ergonomic factors as well as psychological factors such as work-related stress can be both risk factors and prognostic factors for neck pain. [20, 21] As depression and anxiety may be caused or aggravated by job demands, [22] working conditions may modify the interaction of psychosocial factors with neck pain. These factors are therefore also to be considered for assessment and management of neck pain.”
6. Differences between the univariate and multivariate analyses should be discussed, in particular the difference with regard to social support (5.19 crude, -0.49 adjusted!).

We now discuss this finding in the second paragraph of the Discussion section: "Deficits in social support, basic education, and infrequent exercise, in contrast, were not linked with neck pain in the adjusted model. This may indicate that social support and exercise are confounding factors and that variability in neck pain levels is intrinsically explained by psychosocial characteristics."

Minor essential revisions
1. In the abstract and in other parts of the text as well, the authors state that current therapies focus on medicinal interventions. It is not clear where this statement is based upon. For instance in the recommendations of the Bone and Joint Decade Task Force, other therapies were mentioned as well, although none of them were of a psychosocial nature.

We agree with the reviewer that the term “medicinal” is misleading. We rephrased the corresponding sentences using the term “somatically based therapies” instead when on-psychosocial therapeutic options such as exercise, manipulation and mobilisation, acupuncture, medicinal and injection therapies are referred to.

2. Many statements in the article are probably based on the literature, but have no reference. For instance in the discussion section: “psychosocial factors are closely related to cultural and regional factors”.

We added several references (Ref #18-23).

3. The drawbacks of medicinal therapies as described in the background, are not exclusively reserved for this kind of therapy. Psychosocial interventions have their drawbacks too. In general, this part is written a little too toughless.

Thank you for this important remark. We added text to the last paragraph of the Discussion section to point to this aspect: “Of course, not only somatically based therapies but also psychosocial interventions have their drawbacks. [23] Upcoming studies should therefore evaluate not only efficiency but also risks and harms of both types of interventions.”

4. In which form the variables are added to the model, should be described more clearly. Some variables seem to be dichotomized first. The reasons why should be described as well.

We expanded the corresponding paragraph in the Methods section (“Statistical analyses”) to describe the linear regression models more precisely: "Baseline variables included were dichotomous socio-demographic characteristics (age 50 years or older, female, unemployed or retired, basic education, living without partner, living with 2 or less persons in the same household), psychometric characteristics (HADS depression and anxiety subscales, deficits in social support), one medicinal history characteristic (previous cervical spine injury), and one health-promoting lifestyle characteristic (exercise once or less per week). We included the continuous depression and the anxiety subscale of the HADS in the regression analyses to increase power, the F-SozU scale for measurement of deficits in social support was dichotomised because of skewed distribution.”
5. It is unclear how much time passed by between the visit to general practice and the questionnaire.

We specified that on average 3 months passed by between the visit to general practice and the shipping of the questionnaire:

“Participants received the questionnaire from their primary care physicians together with written instructions on average 3 months after the consultation because of neck pain.”

6. In “demographic characteristics of the study sample” it was mentioned that some participants had had previous surgery or a previous injury. It is unclear what was meant with previous. Previous to their visit in March 2005-April 2006 to general practice or previous to the questionnaire.

We clarified that it was asked for surgery/injury previous to completing the questionnaire (Methods section, “Baseline variables”):

“Single item questions were used to ask for injuries of the cervical spine previous to completing the questionnaire...”

7. Apparently, the authors used another measure (or measures) for neck pain as well. In table 1 the frequency of neck pain was presented and in the results of the descriptive analysis it was mentioned that a higher neck pain frequency was related to a higher NPAD-score. This variable should also be described in the methods section.

We apologize for this omission. We added the corresponding information to the Methods section (“Baseline variables”):

“Additionally, three single item questions asked whether or not neck pain was present on the day of questionnaire completion, on more than 100 days in the last year, and whether or not neck pain was constantly present during the last year.”

8. The authors carried out univariate and multivariate linear regression analyses. In addition they carried out analysis of variance. It should be explained why this step was added.

As regression coefficients for continuous independent variables that range from 0 to 21 are difficult to interpret clinically, we used analysis of variance to derive more illustrative results. For explanation, we rephrased the corresponding section of the “Statistical analysis” paragraph in the Methods section:

“The adjusted linear regression analysis revealed that continuous independent variables (HADS depression and anxiety subscales) were significantly correlated with neck pain. As regression coefficients for continuous independent variables that range from 0 to 21 are difficult to interpret clinically, we used analysis of variance to investigate how those scales varied across patients with different levels of neck pain. Therefore, study participants were allocated to the following three groups: (…) Mean values and standard deviations of the two scales were derived to illustrate the crude extent of variation attributable to the level of neck pain.”

9. Results with regard to previous cervical spine surgery only refer to 7 subjects! Due to other missing values the number of subjects in the adjusted analyses may even be smaller. The
difference between crude and adjusted analyses are large. I think it is not sound to include this variable in the analyses.

We agree with the reviewer that, given the small number of cases, it is more appropriate to not include the cervical spine surgery variable in the analyses. We recalculated the models and adapted the corresponding text and tables.

Discretionary revisions
1. In the abstract the NPAD-d is mentioned, without being explained in the previous text.

We added the abbreviation NPAD-d in brackets behind “Neck Pain and Disability Scale” in the Methods section of the abstract.

2. In “Description of the study sample” a response percentage should be given.

We have done that.

3. About the imputation of missing NPAD scores: I assume this was done to increase power. Did the authors carry out a sensitivity analysis or analyses with the unimputed data as well to check for differences?

We added information about sensitivity analyses to the Methods section ("Statistical analyses") and the Results section:

“For sensitivity analyses, we recalculated linear regression models including only those participants with complete answers to all NPAD-d items (350 persons).”

“Sensitivity analyses of crude and adjusted linear regression models including only those participants with complete NPAD-d questionnaires did not reveal substantial differences in results.”

4. In general: the wording of concepts should be checked. For instance the next three points: At several places in the text was referred to “chronic patients”. The term “chronic” should be explained.

For clarity, we replaced the term “chronic” by “recurrent and persistent”.

5. The last sentence of the conclusion: “For successful long term results it is essential to …..”. It has not been mentioned before that results should be considered in the long term. Moreover, the study results do not give indications about results, and certainly not about the period in which they will occur.

We deleted this sentence.

6. The first line of “Crude linear regression models”: “In order to investigate associations of clinical markers with neck pain….”. I am not sure what is meant with clinical markers, but to me the term suggests more objective data like blood test results.
We rephrased this sentence by using the term “other individual characteristics” instead of “clinical markers”.

7. At first sight it is not clear what the numbers in table 3 represent. Something should be added in the title like: “depression and anxiety scores for different levels of neck pain”.

We modified table 3 according to this suggestion.