Author's response to reviews

Title: Symptom load and functional ability: Results from the Ullensaker Population Study

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Revision of manuscript: MS: 1570825767580335 ; entitled “Symptom load and functional ability: Results from the Ullensaker Population Study”, now entitled “Symptom load and functional status: Results from the Ullensaker Population Study”.

We thank you for the opportunity to revise our manuscript in accordance with the important comments from three reviewers. A detailed point-by-point description of the changes made follows, directly addressing each reviewer’s concerns in the order in which they were presented to us.

Referee nr. 1

Major compulsory revisions:

1. (a) On page 7 and in table 2 it says that the explained variance was increased when the symptoms were entered separately (as dichotomous variables??). However this may be an statistical artefact due to overfitting of the model (e.g. Bayak 2004) an aspect which should be at least discussed. Also, measures of fit adjusting for the numbers of variables such as the Baysian Information Criterion (BIC) are available.

In the revised manuscript we have clarified the use of the six different symptom variables as independent variables in the analyses. We described how dichotomous variables vs. number of symptoms perform in models on functional status/COOP WONCA. The article referred to by the referee (1) points to problems arising by overfitting in regression-type models, and ways to guard against overfitting (eg. penalisation and shrinkage). One method described is to present the adjusted $R^2$ to penalise for the number of variables in the model. We have, however, used the $\Delta R^2$ to reflect the unique contribution of each variable to explain the variance in functional status, as described below. Babyak also refers to the sample size estimation of Green, requiring a minimum base sample size of 50 observation + roughly 8 variables per independent variable. The analyses in this paper are well above these limits: the largest model consists of 25 independent variables (the total 23
individual symptoms, age and sex), requiring a minimum of 250 observations.

The referee rightly reminds us that models with different numbers of variables cannot be directly compared through explained variance. In accordance with this comment, we have performed analysis rendering Bayesian Information Criterion (BIC) for all the six models used in functional status. The findings show that the three models with the individual symptoms have the best fit to the data, in comparison to those modelling numbers of symptoms. The ranging of models according to the BIC-values is consistent with the explanatory power found for each model. The models with the individual symptoms have the best fit, as dichotomised variables generally fit into models well, whereas the number of symptoms are not associated with functional status in an absolute linear fashion. We have discussed this in brief in the manuscript as suggested.

1. (b) Also, in such models multiple collinearity is likely so that the contribution of individual parameters cannot be appropriately appraised. This aspect should at least be discussed as well and a measure of multi-collinearity such as VIF may be provided.

Although it was not reported in the manuscript, we performed analyses to check for collinearity-problems between symptoms prior to conducting the regression analyses in the manuscript. The analysis did not reveal problems of collinearity (the largest correlation coefficient was found between the variables anxiety and depression; 0.586). Collinearity statistics rendered Tolerance values or Variance Inflation Factors (VIF) for each symptom that was very well within acceptable limits. All Tolerance values were above 0.9 and all VIF-values were around 1.0. In the manuscript we have referred to the analysis of collinearity, and left the regression model unaltered.

2. Moreover, it is unclear if the multiple correlation coefficient is just the usual determination coefficient (= explained variance through all variables in the model) or the multiple coefficient of determination which is not so well known. Please explain.

In the revised manuscript we have clarified how the presented explained variances are derived. Inspired by this referee, we now present the change in $R^2 (\Delta R^2)$ that represents the contribution to explained variance by each of the variables.

Minor essential revisions

3. I often got confused because throughout the paper different terms are used for the same issue, i.e. pain symptoms, musculoskeletal symptoms, symptoms, muscular symptoms, number of pain sites (NPS) seem to be used synonymous, I would suggest to just use one term and if an acronym is introduced to then consequently use this acronym.
The six symptom variables used have now been explained more clearly. We have numbered the symptom models and we have used them consequently throughout as follows:
Model I: NPS = number of pain sites;
Model II: NN-MS = number of non-musculoskeletal symptoms;
Model III: The total number of symptoms (NPS+NN-MS);
Model IV: All 10 individual musculoskeletal symptoms;
Model V: All 13 individual non-musculoskeletal symptoms;
Model VI: All 23 individual symptoms

4. On page 4 in the last paragraph, it says "regressions on non-muscular symptoms and NN-MS" which I thought were the same. For clarity, please also write regressions of functional ability/COOP-WONCA on ...

These were two different analyses: one modelling the number of non-musculoskeletal symptoms and the other modelling the individual non-musculoskeletal symptoms together (dichotomised variables). We have clarified this passage in the manuscript, and also clarified the six different symptoms variables elsewhere in the manuscript (see point 3 above). We also altered the sentence so that it is clear that the dependent variable in the analyses is functional status/COOP-WONCA.

5. P 6: Please provide the mean age, standard deviation, and age range of the sample in paragraph 1.

This has now been included in the document, stratified by sex.

6. P 6/table 2: It is not surprising that NPS has a higher beta than NN-MS since they are differently scaled with NPS having a smaller range. Please include standardized coefficients.

The referee is quite right, and we have now included the standardised beta-coefficients in Table 2 (now Table 1).

Discretionary Revisions

7. Though not the main focus of the study it could make sense to adjust for socio-economic variables in a separate model. I would expect that the contribution of number of symptoms could then decrease. As reported symptom number and SES may both be correlated with functional ability.

We agree that both self-reported symptoms and SES may be correlated with functional status. The focus of this paper has not been to isolate predictors for functional status, but rather to look at associations between self-reported symptoms and functional status. The study being of a cross-sectional design, we cannot derive causal directions from the associations, and we have suspected
socioeconomic variables to be colliders between the symptom variables and functional status (whereby they should not be adjusted for). For this revision, we have performed analyses including the following socioeconomic variables (SES)
Marriage status 2. Education
3. Employment status
We performed analyses looking at the individual effects of the following components in the six models: 1. Age/sex; 2. Socioeconomic variables (as described above); 3. Symptom variables.

The contributions of all symptom variables in functional status were reduced in adjusting for SES. SES contributed to approximately 16% of the variance in functional status in each model.

In the revised manuscript, we have not included these findings, as this might complicate and lengthen the manuscript substantially.

8. Table 1 is difficult to read and a graphical depiction, e.g. as bar chart with collapsed categories may be an idea.

We have considered different ways in which to present the data from Table 1 in a better way, and have ended up with a new Figure 1.

Referee nr. 2:

1. Abstract, last sentence before Conclusion: The sentence seems unclear to me.

We have altered the sentence in the revised manuscript.

2. Methods, 1. paragraph: The right spelling is “Regional Committee for Medical and Health Research Ethics”.

We thank the reviewer for the correction.

3. Statistical analyses, 1. paragraph: The authors report that they have made imputations, but it would be interesting to know how many missing values they found and how may imputations were performed.

We have reported on this issue in a previous paper (2). The following paragraph describes the procedure and is a quote from that paper. We have accounted for these findings in the revised manuscript.

“A number of respondents only ticked “yes” or “no” for some pain sites (15.3%) and other symptoms (9.0%), and did not tick for the rest. For blank answers we assumed that the
symptom/pain was not present and they were consequently coded as “not present”. Imputations were done for a total of 21.2% of the respondents. To control for how these imputation procedures might influence the results, we performed sensitivity analyses where all analyses were performed on non-imputated data”.

4. In the analyses they have adjusted for age and sex, but not for SES. Was this information not available? If not: why? Would SES be of interest?

We have commented on the effect of socioeconomic variables in the response to Referee nr. 1 (see point 7).

5. Results, 1. paragraph/discussion: The response rate was 54.4%. Do the authors know anything about non-responders? How might the selection influence the results?

We have previously commented on non-responders in a previous paper (2). We refer to these findings in the revised manuscript. The paragraphs below are quotes from this paper.

From results: “The participation rate was higher in women (59%) than men (49%), and higher in middle-aged groups for both genders [14]. Of respondents, 54.9% were women and 45.1% men. The distribution of respondents within age groups was as follows (the percentage within each age group in our census population in parentheses [25]): 24–26: 9.8% (16.5%), 34–36: 29.2% (25.2%), 44–46: 18.5% (18.7%), 54–56: 20.6% (17.8%), 64–66: 13.5% (11.0%), 74–76: 7.0% (7.4%), and 84–86 year olds: 1.5% (3.2%). Accordingly, non-responders are mostly to be found among the youngest and oldest age groups”.

From discussion: “We have no data on symptoms experienced by non-responders and are, therefore, unable to draw conclusions about the representability of participants’ reporting of symptoms. Higher response rates in the groups reporting most symptoms (i.e. women and middle-aged) can indicate that the effect of interest in the study have been more important than the healthy volunteer effect, and this might have caused some overestimation of the prevalence figures”.

6. Results, 2. paragraph/discussion: A mean number of 2.3 pain sites was found. The authors do not discuss if that was a high or low number. Was it comparable to the mean of 3.6 reported from UK? If yes, was the difference of any significance? What might be the explanation?

The results from the two studies are now shortly discussed.

7. Results,3. paragraph: Figure 1 and 2: It would be interesting to see these figures for each gender.
In response to the comments made by all three reviewers Figure 1 is now stratified by sex. As to the relationship between number of symptoms and functional status (Figure 2 and 3) there are only marginal sex differences. Including sex in the figure would not give marked difference.

8. Results, 5. paragraph/discussion: When all 23 symptoms were entered an R² of 60.6% was found. Was that a high or low number, - and compared to what?

In the revised manuscript we are now presenting the change in R² (ΔR²) contributed for by each of the variables in the model. We now state that the 23 individual symptoms contribute to 48.2% of the variance in functional status. The individual symptoms thereby explain more of the variance than the number of symptoms (NPS+NN-MS) where ΔR²=0.392. The individual symptoms also have a better model fit (lower BIC). However, explaining almost half of the variance in functional status must be considered a substantial contribution in explaining functional status, and simply counting the number of symptoms may be an acceptable proxy.

9. Results, 6. paragraph/discussion: In Model II the explanatory power diminished, but the authors do not explain why.

Model II had been renamed Model B. When adjusting for the presence of all other symptoms, the contribution of each symptom in the model diminished. These analyses were initially performed to try to isolate ”key” symptoms to explain variance in health status. The reduction in explained variance in these analyses supports our hypothesis that the total symptom load experienced might be more important than the nature of the symptoms in question.

10. Discussion, 3 paragraph: The authors have previously shown that number of pain sites predicts future disability pensioning. What is the association between subjectively reported functional disability and disability pensioning?

To our knowledge, no studies have directly compared the association between subjectively reported functional status and future disability pensioning. The referee refers to a previous study by the research group, documenting that NPS is a strong predictor for future disability (4). We have also shown that an increasing NPS is almost linearly associated with increasing self-reported functional problems (on four scales in COOP/WONCA, as in the present paper) (5). From these results, we cannot infer that there is a close relationship between self-reported functional status and disability pensioning, but it is a plausible hypothesis.

11. Discussion, last paragraph: It would be interesting if the authors briefly could mention the direction of future research in order to reveal the cause effect.

We have underlined the cross-sectional character of the study and that the purpose is not to seek causal factors for reduced function. As non-musculoskeletal symptoms were first introduced in the questionnaires
in the Ullensaker study in 2004, we will from the 2010 data be able to assess the longitudinal effects of the symptom load on disability pensioning and other health-related outcomes.

Referee nr. 3

Major compulsory revisions

1. The response rate was 53%. When reporting prevalence rates it is of interest whether the responders are representative for the population regarding at least sex and age distribution. If not Table 1 should be stratified for gender and age-groups for aggregated number of symptoms.

We have now reported on the sex and age distribution in the population, by referring to a previous article (2). We have also replaced Table 1 with a Figure (now Figure 1).

2. The sex differences in prevalence rates of reporting symptoms and complaints require stratified analyses on gender. If not presented, at least should the results of such analyses be commented on,

Answered under ref. 2, pt. 7.

3. Under Methods p 2, 1. Sentence: “Functional status was recorded using …”, which is correct. COOP-WONCA assesses functional health status which is not the same as functional ability? The authors should consider using the term functional (health) status throughout the manuscript.

Minor Essential revisions

We have revised the manuscript so that COOP/WONCA scores are now referred to as functional status rather than functional ability.

4. To interpret multiple correlation coefficients in multiple linear regression models as explained variance is not straightforward. In the presented models, not stratified for sex models but adjusted for age and sex, sex would probably contribute to some of the explained variance and not only the number of symptoms included.

To make the contribution of each component in the models clear, we now present all $R^2$-values as changes in $R^2$ ($\Delta R^2$), where the effect of the other components (age and sex) are removed.

5. Being a cross-sectional study, the direction of the relationship between functional status and symptoms could not be stated. Not clearly expressed, but the overall impression from the analyses, presentation of results and the
discussion is that the experience of symptoms affects the functional status. Inherent in a reduced functional status could be experience of both symptoms and complaints? A few word on the two-ways relationship has been welcomed.

We have now underlined that the study is cross-sectional and that the purpose is to look at associations rather than causal effects.

Sincerely yours

Dag Bruusgaard

Hedda Tschudi-Madsen

Reference List


