Author’s response to reviews

Title: Stress levels predict substantial improvement in pain intensity after 10 to 12 years in women with fibromyalgia and chronic widespread pain. A cohort study.

Authors:

Anna Bergenheim (anna.c.bergenheim@vgregion.se)
Sofia Juhlin (sofia.e.johannesson@vgregion.se)
Lena Nordeman (lena.nordeman@vgregion.se)
Monica Joelsson (Monica.joelsson@vgregion.se)
Kaisa Mannerkorpi (Kaisa.Mannerkorpi@neuro.gu.se)

Version: 2 Date: 23 Apr 2019

Author’s response to reviews:

Reply to reviewer:

Thank you for reviewing my manuscript so thoroughly and your comments have improved the manuscript. Below are my answers to your comments:

- You have provided a reference for the recommended use of percentage reduction in pain in clinical trials - could you also please provide a reference that demonstrates its suitability for non-trial situations.

Reply: Thank you for clarifying this point, and we understand your request. We were interested in predictors of a substantial improvement in pain intensity, and not a minimal clinical important difference. To the best of our knowledge there are no commonly accepted limit for substantial improvement in pain intensity in cohort studies.

The suggested limits of 30 % and 50 % improvement have been used previously in another large cohort study in Fibromyalgia (Walitt B, Fitzcharles MA, Hassett AL, Katz RS, Hauser W, Wolfe F. The longitudinal outcome of fibromyalgia: a study of 1555 patients. J Rheumatol. 2011;38(10):2238-46).

There is one reference which suggests minimal clinically important changes for cohorts of chronic musculoskeletal pain, suggesting that 15 % reduction in pain intensity is MCID and a 33 % reduction reflects a “much better” improvement. The reference however refers to a NRS and
not a VAS which is used in our study, but we have not found any suitable reference concerning VAS.


We include these references, along with some further clarification in the manuscript in the background (p.3, line 24) and in the discussion (p.13, line 19).

- You have consulted a statistician who said that having predictors associated with pain intensity at baseline is not a problem because you have used a relative measure of improvement rather than a cut-off - could you please provide a reference for this.

Reply: If we understand the suggested Sorjonen reference correctly it refers to a situation in which some individuals already at baseline are close to a cut-off to be “cases”. This could make individuals who are close to the cut-off at baseline to “fall over the line” at follow-up by chance and thus be defined as “cases” at follow-up. This could give false associations since predictors of pain intensity at baseline then will be predictors of pain intensity at follow-up.

However, in our study, when the dependent variable is improvement over 50 %, it is likely that this problem will be smaller, since all individuals in some meaning are equally far from the cut-off of 50 % improvement. But the problem is not eliminated, due to regression to the mean.

We therefore include baseline pain intensity in the regression model, which reduces the risk of finding false predictors. In the multivariable regression model, both pain intensity and stress are significant predictors of improvement. That is, stress was found to predict improvement also when the baseline value of pain intensity is taken into consideration, which we find strengthens the results.

Hopefully this explanation clarifies our thoughts.

- In the Abstract, page 2, line 16, mean change for pain distribution is -2.0 with no units of measurement. You could write this as '-2.0 sites' or '-2.0 regions', perhaps.

Reply: We have now added “mm” and “sites” in the abstract, thank you.

- In the limitations section of the Discussion, you say that improvement is unlikely to be due to regression to the mean since you ask about pain in the last month. This does not convince me
that this is not regression. Instead you could mention something about how the patients were recruited to the cohort.

Reply: We have now removed the sentence you found questionable. We have also added a section in Limitations in Discussion about the possible limitation of using a cohort which were originally recruited to an exercise study, p. 15, line 23.

- In line 13 of page 11, the association of baseline stress with a reduction in pain intensity in the multivariable model (OR 0.69, 95%CI 0.53-0.89) is exactly the same as that in the univariable model in Table 4 - is that correct?

Reply: Thank you for pointing this out! The numbers in Table 4 for SCI-93 were wrong for some reason, we have now changed the numbers in the table.

- Higher pain intensity at baseline predicts substantial improvement in pain intensity 10 to 12 years later. Would you therefore say "the worse a patient's pain is, the more likely they are to get better"? Please comment on this finding in the Discussion.

Reply: This finding could partly be due to regression to the mean.

Pain intensity was however not found to be a significant predictor of substantial improvement in pain intensity in the univariable analysis. In the multivariable analysis higher pain intensity in combination with lower stress levels predicted improvement in pain. I have now commented on this finding in the discussion on p. 14, line 19.