Author's response to reviews

Title: The long-term effects of naprapathic manual therapy on back and neck pain. Results from a pragmatic randomized controlled trial

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Author's response to reviews: see over
Dear Editor,

We appreciate your positive approach and the valuable comments from the reviewers of our paper 1203721962315147 - The long-term effects of naprapathic manual therapy on back and neck pain. Results from a pragmatic randomized controlled trial.

In summary we think the paper has been improved by clarifying the issues pointed out by the reviewers.

We have made specific replies to the reviewer’s comments, including the ones that you believed required significant attention, and made it clear whether or not their suggestions have been accepted and reasons for rebuttal if not. Appropriate changes have been made in the revised manuscript text, written in red.

Yours sincerely

Eva Skillgate

Reviewer: Mitchell Haas

Reviewer's report:
Major Compulsory Revisions:
1. The paper has multiple primary outcomes. A corrected significance test should be used to account for the 4 outcomes. The confidence interval should either be corrected or a p-value included with statistical significance set at .05/4.

Answer: In general we think that what is important to focus upon is the effect size and to comment on its precision (95% CI). But we have also added the p-values to the tables for those who prefer to interpret these.

The suggestion has led to changes in all tables in the manuscript.
2. Specify that the dichotomized improvement variables are the primary analysis. State if this was planned in advance or not. State if the cut points used to dichotomize the variables were pre-planned or not.

**Answer:** The dichotomized improvement variables are the one used in the primary analysis, and that was planned in advance, as were the cut points used to dichotomize the variables. We have added this information to the manuscript to make that more clear.

*The suggestion has led to changes on page 9 and 10 in the manuscript.*

3. GEE: Why were generalized estimating equations used for dichotomized but not the continuous variables in the analysis? This would seem more appropriate than t-tests. The same reasoning for longitudinal analysis would apply to both types of data.

**Answer:** We performed and presented the GEE analysis with dichotomized variables since that was our main analyses. Nevertheless we did also perform the analyses with continuous variables. These analyses were not presented in the manuscript, but showed that the differences between the groups considered over one year were statistically significant regarding improvement in pain (p<0.0001), and disability on CPQ (p<0.0001) favoring the Index Group.

*The suggestion has not led to changes in the manuscript.*

Clarify whether the confidence intervals for group comparisons are based on the GEE analysis or not.

**Answer:** GEE analysis is suitable when there are repeated measurements in group comparisons. In the group comparisons in the tables, only two measurements are used and GEE analysis is not used.

*The suggestion has not led to changes in the manuscript.*

4. GEE: Why was GEE for the entire study reported in the results section, when the purpose of the report is long-term outcomes?

**Answer:** When the first article was published (Skillgate et al Clin J Pain 2007), analyses taking into account the covariance between repeated measurements were not that often requested, and theses analyses were not reported. Now we know that this is an important issue to address in trials like this. Therefore we wanted to report the result of the whole follow-up period in this second manuscript.

*You should include p-values for the 26- and 52-week time points in the text.*

**Answer:** The GEE analyses that we have reported in the original manuscript include data from all time points which we find most appropriate to give an answer to our research question. Additional analyses with only the 26- and 52-week time points showed that the differences
between the groups considered over the second half year of the study period were statistically
significant regarding an improvement in pain (dichotomized outcome: p<0.0001, and
continuous outcome: p=0.0003 ), and disability on CPQ (dichotomized outcome: p=0.0013,
and continuous outcome: p=0.0005) favoring the Index Group. We have not added this data to
the manuscript.

Also, the GEE analysis in the text appears to be for the entire sample, but Figure 2
showing the longitudinal data separates out neck pain and back pain. Why
show these data separately but present a combined analysis? The lack of
consistency can be confusing to the reader.

Answer: The analyses of back and neck pain patients separately are to be considered as
additional subgroup analyses. We have now added a table (Table 5) with the result of
comparisons of differences in changes in pain and disability between the groups, for back and
neck pain patients separately that we hope have improved the quality of the manuscript. But
we have not done the GEE analyses for the subgroups.

The suggestion has led to a new table (Table 5) and corresponding comments to the table
in the Result section on page 13 and in the Discussion on page 14 in the manuscript.

5. Was an intention-to-treat analysis performed? State in the text.

Answer: Yes, and that was stated in the text. Nevertheless we have made that statement even
more clear by adding that All analysis was performed using an “intention to treat” principle.

The suggestion has led to changes on page 10 in the manuscript.

6. Missing data analysis: There is nontrivial missing data at follow-up. A
sensitivity analysis using imputed data should be performed. A brief description
explaining missing data at follow-up would be helpful.

Answer: A sensitivity analysis was done and is reported in the manuscript. From page 10: “To
estimate the impact of missing responses, additional sensitivity analyses were performed,
using multiple imputations with “predictive mean matching method” “

The result of the analysis is reported in the Results on page 13: “Sensitivity analyses
performed to evaluate potential bias from loss of follow-up showed no systematic differences
in results between analyses with and without imputed primary outcome values.”

Since there seems to be no bias from missing values, we have not discussed that in the
Discussion.

The suggestion has not led to changes in the manuscript.

7. 12-week data: Remove from text and tables. 1. This is a short-term outcome
covered in a previous publication and is not consistent with the purpose of the
paper (long-term outcomes). 2. The text and tables are inconsistent, sometimes including and sometimes excluding 12 weeks.

**Answer:** We have now removed the 12-week data from the tables to make the manuscript easier to read.

**The suggestion has led to changes in table 2 and 3.**

**Minor Essential Revisions:**
1. **Background:** It is true that the Cochrane review (ref. 8) concluded that SMT was no more effective than other treatments. However, the language is misleading, implying that SMT has to be more effected to be recommended as a treatment option. Cherkin et al (ref. 12) concluded that SMT was as effective as other treatment options. Bronfort et al (ref. 7) found quality evidence of similarity and superiority of SMT to other treatment approaches. They concluded that the evidence supports SMT as an option for chronic low back pain. This alternative interpretation should be included. It should be noted that the Cochrane review used meta-regression, while Bronfort et al used a best-evidence synthesis approach.

**Answer:** We have now rewritten this part of the Introduction, and included the alternative interpretation that was suggested. We hope that the message of the evidence regarding SMT now is more clear and correct.

**The suggestion has led to changes on page 4 in the manuscript.**

**Reviewer:** Jerrilyn Cambron

**Reviewer’s report:**

**Major Compulsory Revisions:**
1. The Background section is rather interesting. However, the first paragraph second sentence includes only one neck pain reference (6) even though the paragraph insinuates neck and back literature.

**Answer:** We agree with the reviewer that this need to be clarified, and have changed in the manuscript.

**The suggestion has led to changes on page 4 in the manuscript.**

2. The first sentence of paragraph 3 of the Background section begins the discussion on “spinal manipulation/mobilization.” However, the paragraph then only discusses manipulation.

**Answer:** We agree with the reviewer that this need to be clarified, and have changed in the manuscript.

**The suggestion has led to changes on page 4 in the manuscript.**
3. The Methods section somewhat described the duration of neck and/or back pain as present pain that brought about marked dysfunction for at least two weeks. Does that mean during the previous two weeks or any two weeks in the past year or any two weeks in their lifetime? Also, what is an “acute slipped disc”? Do you mean disc herniation or bulge?

Answer: The inclusion criterion regarding pain was: pain now and the previous two weeks or longer in back and/or neck of the kind that brought about marked dysfunction at work and/or in leisure time. We have changed the text in the Methods section and hope the new wording is better.

We have also changed the expression acute slipped disc to disc herniation.

The suggestion has led to changes on page 6 in the manuscript

4. The index group received six treatments within six weeks and the control group received one treatment which occurred during the examination. Of course there might be some treatment effect due to the attention. Please discuss this limitation a bit more in the discussion section including how this might have affected the results.

Answer: The control group was offered two treatments and the index group six. The non-specific effects of the hands-on approach and the potentially intensive patient-therapist interaction in the Index Group due to more treatment sessions have probably contributed to the results. We do not believe that this difference in attention is the only reason to the results. Specific effects from the manual therapy on the function in the neuromusculoskeletal system probably also contributed. This assumption is made based on the documented effect of two of the manual techniques in naprapathic manual therapy, spinal manipulation/mobilization and massage, respectively.

We have added some discussion about this in the Discussion.

The suggestion has led to changes on page 14 in the manuscript

5. In the Methods section on Statistical Analysis, the authors state that GEE models analyzed the effect on pain and disability. They continue with “The final model included the following terms in addition to the treatment variable…” However, the outcome pain and disability measures were not included in this statement. Should I assume that the pain and disability measures were included in the final model?

Answer: Yes, of course we also had the outcomes in the model to be able to get a result. We have added that information in the manuscript.

The suggestion has led to changes on page 11 in the manuscript.
6. The Methods section on Statistical Analysis states “In the analysis of the outcomes improvement in pain and improvement in disability, subjects with scores at baseline less than required to attain these improvements were excluded.” How many subjects were excluded from analysis? How did these subjects get enrolled in the study in the first place?

**Answer:** As is explained in the Method section: “Potential participants were asked to contact the study administration if they fulfilled the inclusion criteria (pain now and the previous two weeks or longer in back and/or neck of the kind that brought about marked dysfunction at work and/or in leisure time). The study administrator made the first-step exclusions (symptoms too mild, pregnancy, specific diagnoses such as acute slipped disc or spinal stenosis, inability to understand Swedish, and recent visits to a manual therapist with the exception of massage). Subjects fulfilling the participation criteria were scheduled for an appointment at the study center where they gave their informed consent and answered an extensive self-administered questionnaire. Next an experienced physician (one of four) performed a medical examination, made a diagnosis, and prescribed medication if necessary. Further exclusions were made based on the following exclusion criteria: too mild symptoms (the physicians’ subjective opinion based on the estimated pain and disability in the questionnaires filled in before the examination, and the results of the anamnesis and physical examination), evidence-based advice during the past month, surgery in the painful area, acute disc herniation, spondylolisthesis, stenosis or “red flags”.

This means that we included some subjects that had quite mild symptoms. In the analyses of patients with more severe symptoms, these were excluded (Table 3). We cannot give a simple answer on how many subjects that was excluded, since that differs in different outcomes and in different follow-ups. We think that any attempt to add that information in the table makes the table hard to read and understand. But the number of subjects that was excluded can be calculated with information from Table 2 and 3.

Regarding a “Clinically important improvement in pain”, the number of excluded subjects in the groups varied between 4 and 7. Regarding a “Clinically important improvement in disability”, the number of excluded subjects in the groups varied between 12 and 47.

**The suggestion has not led to changes in the manuscript.**

7. The last statement of the discussion states that “We plan to report on the more public health oriented outcomes as cost effectiveness and sick leave as observed in the present trial, when such data have been analyzed.” Why wouldn’t you include that information in the current article? These outcomes are not the primary outcomes of the study and therefore could be included in this current manuscript.

**Answer:** The planned cost effectiveness analyses is part of a PhD-students work, and require extended literature review in this specific topic as well as on appropriate statistical methods. In addition to that we will include information from the social insurance register in Sweden. This is not yet done, thus we have not included this information in this manuscript.
The suggestion has not led to changes in the manuscript.

Minor Essential Revisions:
1. Reference 8 is an older systematic review of manipulation for back pain. The newest is most likely Bronfort et al 2008.

   Answer: We have chosen to refer to both since they use different methods for the systematic review. Bronfort et al used Best-evidence synthesis and Assendelft et al used Meta regression.

The suggestion has not led to changes in the manuscript.

2. In Table 1, please indicate which variables are significantly different.

   Answer: We have indicated which variables that is significantly different in Table 1.

The suggestion has led to changes in table 1 in the manuscript.

3. In Tables 2 and 3, please indicate which outcomes are statistically significant.

   Answer: In general we think that it is more important to focus on the effect size together with its 95% confidence interval since this information is more comprehensive than the p-value. But we have also added the p-values to the tables for those who prefer to interpret these.

The suggestion has led to changes in all tables in the manuscript.

4. In Figure 1, the term “study population” should technically be the “target population” or “general population.” Study population means that all people contacted the research office and were potentially enrolled.

   Answer: We agree and have changed the term “study population” to “Target population” in Figure 1.

The suggestion has led to changes in figure 1.

Discretionary Revisions:
1. Figure 2 included pain and disability scores divided by neck or back pain. However, the analysis and discussion combine the two categories. Is there a reason why the authors did not analyze the data in these categories and compare control and index neck pain groups and control and index back pain groups? This would improve the chances of this clinical trial being used for future systematic reviews on back or neck pain.
Answer: We agree that more information about the subgroups analyses of back and neck pain patients separately may improve the chances to have the article included in future systematic reviews on back and neck pain. We have added a table with that information in the manuscript, called Table 5.

The suggestion has led to a new table (Table 5) in the manuscript.