Author’s response to reviews

Title: No effects of a 12-week supervised exercise therapy program on gait in patients with mild to moderate osteoarthritis. A secondary analysis of a randomized trial.

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Author’s response to reviews: see over
RESPONSE LETTER (MS 1493252269134333):

No effects of a 12-week supervised exercise therapy program on gait in patients with mild to moderate osteoarthritis. A secondary analysis of a randomized trial.

We thank both the Editor and the reviewers for their thorough evaluation and valuable comments to our original manuscript. Rewriting the manuscript in accordance with the given suggestions has clearly improved the quality and readability of our paper. In this response letter, we have successively responded to each comment made. Our response, as well as an explanation for the choice we have made, is given in Italics. We have further specified and underlined the section and page number(s) in the revised manuscript where revised text appears. In the enclosed revised manuscript, all changes made are further highlighted in yellow.

Editorial requests:

Please include the date you received your trial registration next to the registration number.

Author response: Date has been added as required, Trial registration page 3.
Reviewer: Celena Scheede-Bergdahl

Reviewer's report:

Major compulsory revisions:

1) Lack of pre-defined hypothesis: While it is stated in the manuscript that, due to lack of previous work in the area, that there is no pre-defined hypothesis, could a hypothesis not be formulated based on comparable disease conditions? Perhaps, even with OA, previous studies that included exercise training as therapy could be referred to, even without investigating the same end points.

Author response:

This manuscript reports data from a study that was initiated back in 2005. At that time, we did not feel that we could scientifically justify the use of any specific hypotheses in our study. Because the literature on gait in early stage hip OA at that time was more or less non-existent; no consensus existed on which gait variables would be of primary interest. Thus, we considered an exploratory approach including a broad range of variables to be the best available choice, instead of selecting somewhat arbitrary variables to be tested from specific hypotheses. At present time, the literature on gait in early stage hip OA is still limited, and furthermore, characterized by considerable diversity in methods and outcome measures. We do, however, agree that we could have formulated hypotheses with some more support from scientific evidence today. But, as we had chosen an exploratory approach with no pre-defined hypotheses when we did our primary analyses, we feel that it would be ethically wrong to formulate any hypotheses in retrospect – when we already know the study results. Thus, we hope that it can be accepted that we ask to still leave specific hypotheses out of the manuscript. We have, however, extended our reasoning for not formulating specific hypotheses, and we hope this might be clarifying. Changes appear in the last paragraph of the Introduction, page 4.

2) Training specificity: The authors do not discuss how the test measures reflect the exercise training protocol. Perhaps the testing did not accurately reflect how each subject trained, therefore potentially missing benefits obtained. Did the exercises performed reflect the same muscle groups/activation patterns that would be detectable during gait analysis? This needs to be addressed in text.

Author response:

We acknowledge the reviewer for bringing up this important issue; which reviewer 2 also did question. As stated in the original manuscript, specific gait training was not part of the exercise therapy program. Whether our outcome measures thus could be expected to reflect changes is a very relevant question. We have tried to accommodate the concerns raised by both reviewers by adding more text in the Discussion, pages 12, 13 and 14, and furthermore a new reference (ref #24), page 13.

3) How were the individualized training prescribed? Was there a guideline that defined which exercises, dosage and progression was prescribed for each
patient in order to give comparable exercise programmes? How was adherence to program monitored? Was there any control for exercise conducted outside of those prescribed for study? Especially considering that there is a gap in the literature pertaining to dosage for this patient population (as discussed in manuscript), this information could be useful.

Author response:

We do agree that the information requested by the reviewer is clarifying. We have, therefore, included a more detailed description of the guidelines for the exercise therapy program, including dosage and progression in Methods, subheading Interventions, page 7. In addition, the reference to the paper by Fernandes et al. (Ref #13) is kept, so that readers know where to find the full protocol for the interventions.

4) Why was the study compliance so low? It would be interesting to know why subjects did not adhere to program, especially for clinicians who wish to implement similar programs.

Author response:

The low adherence in the exercise therapy group is definitely a concern. We fully agree with the reviewer that it would be of the highest clinical interest to know why patients are not compliant – especially because this also has been a problem in many other training studies. Unfortunately, we did not register the reason for why patients were not attending the required number of training sessions per week; except one patient who did not complete the full program due to increased hip pain. We have added information on our lack of registered reasons for non-compliance in the Discussion, page 12.

5) Were there any reductions in pain due to intervention? Or improvements in physical function (ie: ability to walk, pain free) that could be reported? Other measures, such as the 6 minute walk test, could give important insight into possible improvements in physical function?

Author response:

As this is a substudy of a larger RCT, several other papers based on the overall material have been published. Fernandes et al. (ref #5) and Svege et al. (ref #10) have both included results on self-reported WOMAC scores from the overall RCT. Both studies are referred to in the present paper, and we have also explicitly mentioned that WOMAC physical function, but not pain, was shown to improve in the exercise therapy group (pages 13 and 15). Furthermore, other secondary outcome measures related to impairments and activity limitations (range of motion, muscle strength, 6 meter walk test, and pain during walking) have been investigated in a recent study. However, this manuscript is currently under revision in another scientific journal, and results can therefore unfortunately not be referred to at this point.

We deliberately did not include analyses of other outcome measures than gait variables in this present paper for three reasons: 1) The material included in the biomechanical substudy is underpowered to evaluate group differences for any other outcome measures, 2) To avoid salami publication, and 3) To reduce the problem of statistical multiplicity. We
can therefore not include such data in this paper. However, we absolutely agree that it is of high interest – and look forward to the publication of the paper investigating impairments and activity limitations.

Minor essential revisions:

Manuscript would benefit from English grammatical review.

Author response:

Manuscript has been proofread, and we have to our best ability tried to eliminate grammar mistakes.

In flow chart, check the box "excluded from analysis": during is misspelled.

Author response:

Misspelling corrected, Figure 1.
Reviewer: Trevor B Birmingham

Reviewer's report:

The paper describes a secondary analysis of an RCT for patients with hip OA and mild-to-moderate symptoms. It shows that the addition of an exercise program targeting muscle strength, physical function, neuromuscular control and flexibility did not affect hip, knee and ankle joint angles and moments during walking. Findings are novel. Limitations are acknowledged. I have the following "Minor Essential Revisions" and suggestions that the authors can be trusted to address.

Abstract:

Please add some sort of brief description of the intervention - “exercise therapy” (i.e. something to show that it focused on strength, neuromuscular control and flexibility rather than being an aerobic exercise program)

Author response:

Changed in accordance with the reviewer’s suggestion; Abstract, subheading Background, page 2.

Please specifically state “hip, knee and ankle” joint

Author response:

Added in accordance with the reviewer’s suggestion; Abstract, subheading Results, page 2.

Conclusions about “any biomechanical changes” and “gait alterations” are likely too strong given what was actually measured. I suggest more precisely stating no changes in hip, knee, ankle joint angles and moments during walking

Author response:

Changed in accordance with the reviewer’s suggestion; Abstract, subheadings Results and Conclusions, page 3.

Main Text:

Background:

Stating the specific measures that were the “distinct gait alterations” and relating them to the present study would be helpful either here or in the Methods or Discussion

Author response:

Changed in accordance with the reviewer’s suggestion, Background, page 4.

Methods:
Regarding the stated power / sample size calculations, please add information about the effect size - i.e. what size of an effect (how much of a difference between groups) did the 21 patients provide the 90% power to detect? Also, I assume alpha was set at 0.05?

Author response:

The power estimations in this study were challenging. At the time of study initiation, literature was very limited, with a lack of consensus on what gait variables were of most interest. Further, no data from hip OA patients at a comparable level of disease could be used for deciding a cut-off for minimal clinically important changes. Therefore, power estimates were based on a previous study from our research group on patients with knee injuries, and we set a 10% difference in knee- and hip joint angles as the treatment effect. We admit that our power estimate thus was somewhat imprecise. In addition to adding the information requested by the reviewer, we have therefore also added more critique to our power estimates. Responses appear on pages 5 and 6. Furthermore, we have also added these concerns in the Discussion, subheading Study limitations, page 16.

Subject characteristics:

Typo: bodyweight

Author response:

Misspelling corrected; Methods, subheading Subject characteristics, page 8.

Analysis:

I suggest the sentence about normalizing to percent stance be incorporated into the gait analysis, data processing paragraph where the events are defined.

Author response:

Changed in accordance with the reviewer’s suggestion; Methods - Gait analysis, page 9.

Please explicitly state, that the mean of the walking trials was calculated for each subject for each dependent variable (if that was the case) and used in the analyses. Please also specifically state that the figures are showing the mean of all subjects (i.e. are ensemble average curves, mean waveforms, etc.).

Author response:

Added text as suggested by the reviewer; Methods, subheading Gait analysis, page 9.

Results:

Understanding the results of the “correlational analysis” for compliance issues suggest no effect, does evaluating the subgroup of patients who were compliant provide more insight (i.e. did the 9 subjects who met the compliance criteria
experience changes in the dependent variables)?

Author response:

*We did not include separate analysis of the 9 subjects who were compliant, as these analyses would be underpowered. However, we do acknowledge that our presentation of the results from the correlation analysis might have been unclear. We have therefore added a sentence explicitly stating that we did not find support for larger changes among the compliant patients than the non-compliant in the Results, page 11.*

Tables 2 and 3:

If I understand correctly, these tables show the baseline, follow-up and change scores within the two groups, while the F, p and partial eta squared values are from the ANCOVA that compared the follow-up values between groups while controlling for the baseline values. I think many readers will not pick up on that and I suggest that it should be described more precisely – perhaps as a table footnote?

Author response:

*We agree with the reviewer’s comments, and have added explanations to the column headings as a footnote in both Table 2 and Table 3. Furthermore, after discussing with a statistician, we suggest to remove the F-column from the Tables – as it for most readers does not add much information. Removing it, we emphasize the pre-post values within each group; and restrict the results from the ANCOVA to the p-value and the effect size. Hopefully this makes interpretation easier for the readers.*

Discussion:

First paragraph, last sentence. Similarly, given the negative findings, further discussion of the effect sizes, and precision around them, is likely warranted. Strictly speaking, I don’t see “precision estimates” for the effect sizes -although the exploratory nature of the study is duly noted.

Author response:
As previously described, we have tried to address the uncertainty related to our power estimates and the potential consequences for our results more explicitly in this revised paper, both in the Methods section and the Study limitations. The text added in the Discussion, subheading Study limitations, page 16, will hopefully be an adequate response also to the concern mentioned above. It should be noted, that even if we clearly see that our power estimates were not as precise as they ideally should have been, the number of included patients in the present material still make it the largest existent biomechanical study on early stage hip OA to date. Furthermore, as illustrated in Figure 2 and 3, the curves of mean gait characteristics pre- and post intervention in both groups are more or less indistinguishable. Thus, in our opinion, it seems doubtful if a larger study sample would reveal clinically relevant differences. Nevertheless, we fully agree that it is important to discuss the possibility that our methodological choices might have influenced the results, and we hope the revisions made to the manuscript are satisfactory.

Second paragraph, last sentence. True. It is also possible that other biomechanical, gait characteristics were affected and not detected with the present methods. Without belittling the present measures, there should be some sort of acknowledgement that these measures may not reflect plausible changes as a result of the exercise program, such as changes in neuromuscular control and muscular contributions to joint loading, that may change without altering joint angles and moments.

Author response:

We acknowledge this important comment, which also is in line with comments from the first reviewer. As mentioned in our responses to bullet point 2) from the first reviewer, we have tried to accommodate the concerns raised by both reviewers by adding more text in the Discussion on pages 12, 13 and 14, and furthermore a new reference (ref #24), page 13.

Also, perhaps the fact that the “distinct gait patterns” that were previously found to be different in hip OA could be mentioned here or later in the discussion (i.e. were unaffected by the intervention) and help justify the current measures.

Author response:

Sentence has been added with referral to the specific alterations described in the paper by Eitzen et al. (ref #3), Discussion, page 12.