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

Dear Editorial Team of Journal of Negative Results in Biomedicine,

Thank you for giving us the opportunity to submit a re-revised version of our manuscript

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 are pleased to note that our first revision improved the manuscript, and that Reviewer 1 found the manuscript suitable for publication after our first revision. We acknowledge the remaining concerns raised by Reviewer 2, and have to our best ability tried to address these in this re-revision by adding information in the manuscript. Some of the concerns raised were difficult to include in the manuscript, due to the data we have available – even though we agree that the questions are relevant. In these cases, we have tried to clarify and explain why we are not able to include specific information in the text.

In addition to the comments raised by Reviewer 2, we have, after thorough double-checking of our graphs and tables, discovered that we had made a mistake in our presentation of the sagittal plane hip moment graph in Figure 2. This graph should have been presented in the opposite direction. Consequently, this graph has been flipped, and corresponding numbers for sagittal plane hip moments in Table 3 accordingly updated. Unfortunately, we have realized that we in our previously published paper from 2012 (reference #3) made the same mistake in the interpretation of the sagittal plane hip moment. In this paper, we described that hip OA patients compared to controls revealed a reduced external hip flexion moment. This should have been reported as a reduced external hip extension moment. A correction will be submitted to the journal who has published our previous paper to clarify this. As we refer to this finding also in this manuscript, we have changed the text so that we now state that our finding in the previous study was a reduced external hip extension moment. Changes appear in this revised manuscript in the Background, page 4, and Discussion, page 12. We apologize for this mistake, but are glad that it was discovered at this point, so that we are able to both correct our previous publication and present correct interpretations in this revised manuscript.

Furthermore, we have decided to report our frontal plane data in Figure 3 with adduction as positive values and abduction as negative values, as this is a more common way of reporting in the literature. Thus, we have converted the explanation arrows for positive and negative values under Figure 3, and made sure that the Tables are updated accordingly. The changes described do, however, not influence the analyses or results in this manuscript.

Detailed information on our responses to the suggestions from Reviewer 2, and subsequent changes to the manuscript, is provided in this document. To assist the review team in their further reading, we have highlighted all changes in yellow in the manuscript file, and further also specified in this response letter in which paragraph and on which page(s) changes appear.

We hope that the re-revised manuscript may be regarded adequate for publication.

Oslo, Norway, November 14th 2014.

Yours sincerely
Ingrid Eitzen, PT, PhD
Reviewer’s report

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.

Version: 2
Date: 9 October 2014
Reviewer: Celena Scheede-Bergdahl

Reviewer’s report:
Major compulsory revisions:
Thank you for your corrections. Although, they do add to the quality of the manuscript, some outstanding issues remain.

Overall comment: Text still requires revision for English language.

Author response: Paper has been proof-read and edited by a native English speaker familiar with academic language. We do hope that the quality of written language now is acceptable.

In abstract: brief reference to exercise protocol should be given (ie: X weeks of program, consisting of XXX), especially since the authors conclude that they did not find evidence to support that their exercise program was not an efficient intervention to induce gait alterations in this population. In this case, the reader should be provided with some insight into the exercise program employed.

Author response: We absolutely agree that readers must be thoroughly informed about the intervention, but it is limited how detailed we can be within the format of an abstract. The duration of the program (‘12 weeks’) and a brief description of the content (‘The exercise therapy program comprised exercises targeted to improve muscle strength, physical function, neuromuscular control and flexibility’) was included in the Introduction section of the abstract after the first revision. We have in this new version added the number of sessions participants were intended to perform each week, in Abstract, page 2. We are not, however, sure how we can add more information on the exercise therapy program without mentioning specific exercises – which in our opinion would be outside the scope of an abstract.

Do the authors still believe that exercise interventions may be useful? Any suggestions, based on this work?

We have added a sentence in the Conclusions of the abstracts, emphasizing that our exercise therapy program was generalized, not primarily emphasizing gait, and that future studies tailored specifically towards alteration of gait in early stage hip osteoarthritis are warranted. We hope this addresses the concern of the reviewer. Changes appear in the Abstract, page 3.

With regard to whether we still believe exercise interventions to be useful, we think it is difficult to include any comment on this in the abstract. Our data does not support our exercise therapy program to alter gait in patients with mild to
moderate hip OA. Thus, we need to be careful with statements regarding whether we still believe exercise therapy to be an efficient intervention to alter gait – this will potentially be speculative. The topic is, however, thoroughly considered in the discussion on pages 13-14. We have added the following sentence at the end of this part of the discussion to emphasize even further that current knowledge is inconclusive: ‘Future studies addressing specific, tailored exercises intended to alter evident gait deviations in early stage hip OA are thus warranted’. Discussion, page 14.

Introduction: I appreciate the reasons why the authors did not want to include a hypothesis but the justification in the text begs the question whether the authors were of the mind that the program would work or not? Did the authors think that the program would work? Reference 13 could have provided justification, even for a feasibility standpoint.

Author response: At the time this study was initiated (2005), evidence for gait alterations among hip OA patients with mild to moderate symptoms were more or less non-existent. The biomechanical substudy was included as part of the overall RCT in order to 1) describe gait in this particular population of hip OA, and 2) explore whether a general exercise therapy program could alter gait. Based on the fact that we really did not know the extent of gait deviation in this population when the study was initiated, we must state that we actually did not know what to expect – and that our approach thus was exploratory. To clarify, we have added a sentence emphasizing the main purpose of the RCT (to evaluate self-reported pain as main outcome), and furthermore added to the last sentence in the Introduction to specify that we did not hypothesize whether the program would influence gait or not. Changes appear in the Background, page 4.

Methodologies: I am still concerned about the exercise program used versus the analysis conducted. Firstly, more detailed information regarding the exercise program should be provided in the text and not referred to in another article (which is a case study- ref. 13). As this is a negative result, the reader must be as informed as possible to the protocol in order to be certain that the lack of results are not due to study design issues. Looking at reference 13 (Fernandes L et al., 2010), it is still not certain whether measuring gait parameters best reflect the type of exercise prescribed.

Author response: We do agree with the reviewer that it is not certain whether measuring gait parameters best reflects the type of exercise prescribed. As explained in the Methods, the main outcome measure of the overall RCT was self-reported WOMAC pain, and the exercise program was developed in line with current guidelines for lower limb OA treatment; with exercise therapy as a first line treatment to reduce pain and symptoms and improve function. Gait biomechanics was included as a secondary outcome, from an explorative approach. If the study originally had been designed to assess gait as the primary outcome, the content of the program should probably have included specific gait training.

We also agree that it is important that detailed information about the content of the exercise therapy program is provided. However, as the protocol for the exercise therapy program has been published in a separate study, including an appendix...
describing the exercises included (Fernandes et al, 2010, reference #13), and the exercise therapy intervention furthermore is described and discussed in the paper reporting the primary results from the main RCT (Fernandes et al 2010, ref #10), we need to be very careful not to duplicate text and/or content that already have been published by our research group. This could be authorial misconduct in the form of self-plagiarism. For this reason, we have deliberately referred to the two previous publications for detailed descriptions of the exercise therapy program. We do believe that publication of protocols from randomized controlled trials are intended to serve the purpose of providing a detailed description of the intervention – and, hence, that subsequent papers reporting results should refer to the originally published protocol. We have, however, in this revision tried our best to accommodate the requests from reviewer 2 in the following questions (see below for responses to each request) related to the exercise intervention, but within the constraints given by what already has been described in detail in the two mentioned and referred studies (#10 and 13) from our research group.

What control was given as to whether the exercises were performed or not? For example, in the Fernandes et al., 2010 article, there is indication that some exercises were not regularly performed (or performed at all). How was this dealt with in the present study?

**Author response:** There were 26 exercises included in the total pool of exercises. The exercise program was individually adapted to each patient. It was not necessarily intended that all patients should perform all exercises included in the total pool of exercises. Rather, the exercise program was individually customized - within the standardized framework of the protocol. Thus, numerous combinations of exercises were executed within the patients in the exercise therapy group. We do not think that it would be clinically feasible to have all patients performing the exact same program, without taking into account individual differences and adjustments. However, we acknowledge that this approach do imply the possibility that the content of the exercise therapy program may have differed some between patients. Patients were, on the other hand, instructed to always include a set of exercises addressing each of the areas muscle strength, physical function, neuromuscular control and flexibility. We have added a sentence clarifying this in the Methods, page 7.

Would the lack of performance of these exercises affect the gait? Why the lack of execution of these exercises?

**Author response:** Whether some of the exercises in the program could have more impact on gait than others, was beyond the scope and power of this study. Thus, we cannot perform separate analyses on an individual patient level. With the exception of warm-up on the treadmill, no exercises specifically targeting gait were included in the pool of exercises. Patients who experienced increased pain while walking on the treadmill could choose bicycling as warm-up instead. It may be speculated that this could have led to less changes in gait, as patients during walking were informed of the importance of equal cadence and full hip extension while walking. This remains, however, speculative, and we have no data to support this possibility. Thus, we do not think it is adequate to add any further discussion in the text regarding these issues, other than what is already included in the Discussion and
Limitations (lack of targeted specific gait training). Furthermore, pain during walking was not a prominent symptom among the patients in this study. The patients had mild to moderate symptoms, were not candidates for THR, and were before enrollment to the study physically active several times a week.

What difference may have existed if the patients were required to come in the 2 x per week?

**Author response:** As reported in the original manuscript, we did not find any association between the number of exercise sessions completed and gait variables. Thus, our data does not suggest different results in patients who were adherent to exercise 2 x per week. Elaborated related explanation is provided below in the next reviewer comment.

It must also be noted that the poor compliance for the exercise program may have resulted in the study group not being adequately trained, therefore no detectable differences in chosen measurements parameters. This puts into question the conclusions reached in this paper, as is postulated by the authors themselves on page 12 of manuscript (The lack of treatment effects on gait could be reflecting lack of adequate participation rather than the lack of efficacy of the program itself). The results may not have been significant because the sample size was so low, compared to what was suggested by the power calculations.

**Author response:** We acknowledge the low adherence to the exercise program as a limitation to this study. The reported results are based on an intention-to-treat analysis. As the compliance in the exercise therapy group was unfortunately lower than intended, the intention-to-treat approach may conceal changes among those who actually were compliant. However, utilizing a per-protocol analysis was unfortunately not an appropriate alternative, as this analysis would be underpowered with only n=9 patients fulfilling the criteria of minimum 2 weekly training sessions. We therefore conducted an additional correlation analysis to evaluate whether post-intervention gait characteristics were associated with the number of completed training sessions. However, this analysis did not suggest any association (as described in the manuscript in Results, page 11, and Discussion, page 12). From our data we cannot see any trend towards larger changes in those compliant. In the discussion we suggest both the low compliance and the content of the program as possible explanations for the negative results (Discussion, page 12). We have elaborated the possibility of sample size as a limiting factor by adding the following sentence: ‘A larger study sample may, however, be required in future studies in order to provide robust findings as to whether improved adherence may influence gait’ (Discussion, page 13).

Discussion: Again, could the results acquired from previous work (ie: Fernandes et al., 2010) provide some insight into whether the exercise program was expected to be feasible? Perhaps a set of pilot data could have served this purpose?

**Author response:** The feasibility of the exercise therapy program was evaluated before the initiation of the randomized trial, with main focus on pain regulation and
time consumption. Gait data was not included in the reported case study. We do not have any other pilot data at group level on any of the outcome measures; and can therefore unfortunately not provide any further discussion on this subject.

As a reader of this paper, I am not convinced that the lack of significant results stems purely from the inability of this exercise program (or any exercise program) to provoke ameliorations in gait parameter measurements.

Author response: We agree with the reviewer that it is difficult to identify the exact reason(s) why the program did not induce changes in gait. We have suggested both compliance and content of our program to be possible reasons, as well as now also emphasizing the potential need for a larger sample size (Discussion, page 13). Still, as we have tried to implement in the discussion – our findings in are in line with several other studies involving patients with knee OA (no studies exist on hip OA). Furthermore, even in studies explicitly targeting gait, results are not convincing. We have also emphasized this more by stating that ‘Future studies addressing specific, tailored exercises intended to alter evident gait deviations in early stage hip OA are thus warranted’ (Discussion, page 14).

We do agree that we cannot conclude that exercise therapy cannot influence gait – however, we still think that the true conclusion from our study is that our exercise therapy program – conducted as described – did not alter gait characteristics. Hopefully, the study limitations stated, as well as the changes done in this revision, makes this distinction clear to the reader. We have further added the word ‘generalized’ in the conclusion so that we now refer to our program as ‘a generalized 12-week exercise therapy program’; Conclusion, page 17.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being Published

Author response: Paper has been proof-read and edited by a native English speaker familiar with academic language. We do hope that the quality of written language now is acceptable.

Statistical review: No, the manuscript does not need to be seen by a statistician.