Author's response to reviews

Title: Improvements in gait characteristics after intensive resistance and functional training in people with dementia: a randomised controlled trial

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Author's response to reviews: see over

To the editor and reviewers:
We appreciate the reviewers’ and editor’s suggestions for improvement of the manuscript. We have now introduced modifications according to comments made, and added a detailed and comprehensive response on every reviewer comment below. As suggested by reviewer 2 we have added gait variability as an outcome parameter. For addressing the statistical questions we have consulted a statistician (Stefan Englert) from the Institute of Medical Biometry and Informatics, University of Heidelberg, Germany. We have added him as a co-author to the paper since he has substantially contributed to the revision of this paper.

We provide 1.) a marked-up version of the paper with all track changes visible 2.) a clean copy without visible track changes, and 3.) a point-by-point reply to all queries raised by the reviewers. The manuscript has been correctly formatted according to the BMC Geriatrics journal style (based on the word.doc template provided by BMC Geriatrics). We hope we now accomplish the high quality standards of BMC Geriatrics.

Sincerely,
Michael Schwenk

Reviewer: Sarah Lamb

Reviewer's report:
Thank you very much for asking me to review this paper. This is an important topic as so many health professionals believe that people with dementia have little or no rehabilitation potential. These data, if robust, demonstrate that in the short term at least it is possible to improve gait parameters. I have some concerns with the data presented. Major issues

1. The main issue with the paper is selection bias and whether the data can be considered a random sample or not. The authors describe a parent study of 122 people, and the sample for the submitted manuscript as being 61 of those original participants. They provide no explanation as to why there are only 61 of the original participants, and any selection criteria that might have been made with the gait assessments. It is unclear whether in essence the 61 people represent those who were retained for follow up or had particular characteristics that made them eligible for the gait assessments, or were from one particular centre where gait assessments could be performed. This needs to be clarified.
Answer: This has now been clarified in the paper (page 7, line 4-6). The 61 participants of this study have been consecutively recruited (participant 62-122 of the parent study). The electronic GAITRite system required for the gait analysis presented in this paper was available only during the second half of the parent study due to a delay in funding. Thus, gait analysis could be conducted only in a subsample of participants recruited for the parent study. No selection criteria other than the inclusion criteria for this RCT (as reported in the study population section on page 7) were used for the participants included in this study. The progress through the phased of screening, enrolment, allocation, follow-up, and data analysis is comprehensively illustrated in figure 1. The authors apologize for not having clarified this in the previous version of the paper.

2. With only 50% of the original randomised sample remaining in the study, the case that this remains a random sample is questionable. To use significance tests to establish that there is no statistically significant difference between the groups at baseline is not sufficient to confirm a random sample, and is methodologically incorrect (Altman D.G., (1999) Practical Statistics for Medical Research London Chapman & Hall/CRC). The important things to establish are whether the data are missing at random, or whether there are patterns to the missing data. If the data were missing at random, then as a very basic indication, you would expect the proportions of people in the intervention and control arms to be the same, and from the data presented this does not look to be the case. It is difficult to be exactly sure as the information on the original sample is missing.

Answer: We randomised the group participation according to established proceeding (urn design, Wei LJ: A class of designs for sequential clinical trials. Journal of the American Statistical Association 1977, 72:382-386) as described in the paper (page 7, line 23). Despite uneven subgroups sample baseline comparison between study groups showed no significant differences in descriptive parameters or gait parameters. The authors are aware that from the fact that no significant differences were observed it cannot be derived that no such differences exist. The imbalance in study participants in the control and intervention group indeed is obvious, although, the urn design is used to avoid unbalanced numbers. We have verified the randomisation procedure and we have no comprehensive explanation for the uneven distribution. With a certain chance such uneven distributions can happen despite the selected randomisation technique. The randomization was stratified according to sex and location of recruitment (hospitalized vs other). The sequence was concealed until interventions were assigned after baseline measurements (added to page 7, line 24). A person unrelated to the study performed the randomization procedure and assigned participants to their study group.

We stress the fact that no patients recruited and randomised to this study had been excluded from measurements or data analysis after randomisation! The progress through the phased of screening, enrolment, allocation, follow-up, and data analysis is illustrated in figure 1. Those patients which discontinued the study including the cause of drop-out are listed in the manuscript (figure 1). Number of patients who did not finish the study was even in both study groups and mirrors the fact that the participants were old, multimorbid patients with dementia, most of them suffering from acute illness.
As mentioned in the first answer (see comment above), participants of this study have been consecutively recruited (participant 62-122 of the parent study). Therefore, the participants of this study represent a random sample of the studied population of patients with dementia. Likewise, the first 61 patients that could not be included into this study, i.e., so to say with missing data on all endpoints, also represent a random sample from the same population. Therefore, the applied statistical methods are valid; the statistical property of missing at random as defined by Little, Roderick J. A.; Rubin, Donald B. (2002; Statistical analysis with missing data (2nd ed.). New York: Wiley. ISBN 0-471-18386-5) is fulfilled.

3. I would be particularly interested to know whether retention in the intervention and/or control arms are related to adherence/attendance or experience of the intervention at the intervention.

Answer: We did not measure the retention of training effects (no follow up for measuring sustainability of training effects). Measurements were performed before training and at the end of the intervention period, but we did not follow up patients after the end of training. Based on the reviewers comment we have calculated whether improvement in gait performance (gait speed) in the intervention group is related to adherence. We did not find a significant relationship between adherence (percentage of training sessions successfully performed) and improvement in gait speed ($\beta = 0.117$, $R^2 = 0.014$, $P = 0.624$) (added to the manuscript, page 13, line 11). The limited relationship may be related to a ceiling effect in adherence. Adherence to the intervention was excellent in the intervention group (91.9%). As already demonstrated in the paper (page 13, line 5-7), training response was related to lower functional status at baseline. These findings suggest that the most functionally impaired patients reaped the most benefit of the intervention (see discussion page 18, line 4).

4. There is substantially less variability in the measures in the baseline measures in control group than the intervention group.

Answer: Patients had been randomized to both groups using an established procedure (see comment 1+2 above). Variability in motor performances is high in our sample of geriatric patients with dementia. With a certain chance such uneven distributions can happen despite the selected randomisation technique.

5. Having said that, the groups appear reasonably well matched. There is a difference in age (2 years) and a small difference in the number of fallers. Testing that the results are not sensitive to these differences at baseline by using an analysis of co-variance (or equivalent) would be helpful.

Answer: Based on the reviewer’s suggestion we have tested whether the difference in age and number of fallers (based on descriptive results) influence our outcomes (by adding age and number
of fallers as a covariate in our analysis). Adding age as a covariate did not affect our results indicated by similar p-values for our analysis for estimating intervention effects (Speed P ≤ 0.001, Cadence P = 0.002, Stride length P = 0.009, Stride time P = 0.002, Double support P = 0.001, Step width P = 0.962, step time variability P = 0.490, walk-ratio P = 0.614). Also, adding number of fallers as a covariate did not affect our results indicated by similar p-values for our analysis for estimating intervention effects (Speed P ≤ 0.001, Cadence P = 0.002, Stride length P = 0.009, Stride time P = 0.002, double support P = 0.001, Step width P = 0.957, step time variability P = 0.441, walk-ratio P = 0.576).

6. Some of the data in Table 1 are not correctly reported and need checking for example in Line 2 under women the proportions appear as a SD.

Answer: The proportion of women has been corrected (%). Thank you. We have confirmed other data in Table 1.

7. The co-variate adjustment needs greater description, and should include the baseline value of the variable being reported.

Answer: We have clarified the co-variate adjustment in the statistical section (see page 10, line 18-20). As requested by the reviewer, the baseline values of the total sample are now reported in the paper (see legend of table 2). The statistical procedure used in this study represents an established method for analyzing intervention effects, and has been used in previous high-quality studies (e.g. Schoene, D., S. R. Lord, et al. (2013). "A randomized controlled pilot study of home-based step training in older people using videogame technology." PLoS ONE 8(3): e57734.)

8. Some of the data in percentage change column are incorrectly computed. Report the absolute difference between the groups with a 95% confidence interval for the difference (not the change from baseline) as the main estimate of effect.

Answer: The mean treatment difference (adjusted for baseline value) between the groups with a 95% confidence interval is now reported in Table 2. Additionally, we have corrected the % change from baseline values in Table 2. Figure 2 which had displayed the relative change from baseline (calculated as the mean value of the changes from baseline from each single individual) has been deleted, because it does not display the mean treatment difference, which is the main estimate of effect.

9. The effect size calculations are new to me, quite different from a standardised difference, and I fail to see how a difference of 16 seconds over a walk which is taking on average 138 seconds, equates to very large effect size. It seems to equate to a difference of 0.33 in the baseline standard deviation, which would be considered small to moderate by most other reckoning.
Answer: 1) Please note that the difference in gait speed is not expressed in seconds but in centimeter/seconds (=unit for speed). 2) Partial eta square is an established effect measure to describe effect sizes in multivariate ANOVA models and has been used in various trials before (e.g. a) Lemmey, A. B., S. M. Marcora, et al. (2009). "Effects of high-intensity resistance training in patients with rheumatoid arthritis: A randomized controlled trial." Arthritis Care & Research 61(12): 1726-1734. b) Mak, M. K. and C. W. Hui-Chan (2008). "Cued task-specific training is better than exercise in improving sit-to-stand in patients with Parkinson's disease: A randomized controlled trial." Movement Disorders 23(4): 501-509.). Also, the parent paper has used the same statistical approach (ANCOVA with baseline adjustment, eta squared effect sizes; Hauer K, Schwenk M, Zieschang T, Essig M, Becker C, Oster P: Physical training improves motor performance in people with dementia: a randomized controlled trial. J Am Geriatr Soc 2012, 60(1):8-15.) . Partial eta squared characterizes the amount of variance explained by each single variable included in the statistical model. In the originally submitted article we used the partial eta square to describe the treatment effect adjusted for baseline.

Although partial eta squared is a valid effect measure in this univariate setting, as the reviewer pointed out, the readership of BMC Geriatrics might expect a different effect measurement. We, therefore, replaced in the revised manuscript partial eta square by Cohen’s d calculated as: adjusted mean treatment difference/pooled standard deviation (see Table 2). We have used the SE of the adjusted mean treatment difference (provided by SPSS) to back-calculate the pooled SD of the adjusted treatment difference by using the formula: SD = SE * (1 / sqrt(1/n1 + 1/n2) ). n1=sample size intervention group, n2= sample size control group.

The adjusted mean treatment difference for gait speed in our study is 18.3 cm/sec (see new table 2 in manuscript). The corresponding effect size is large (d = 1.27), which confirms our findings from the effect size used previously (partial eta square: 0.292).


The adjusted mean treatment difference found for gait speed in the present study substantially exceeds results from a recent meta-analysis on exercise effects on gait speed in patients with dementia (mean difference 6cm/sec, Potter R, Ellard D, Rees K, Thorogood M: A systematic review of the effects of physical activity on physical functioning, quality of life and depression in older people with dementia. Int J Geriatr Psychiatry 2011, 26(10):1000-1011.) (see page 14, line 22).

Level of interest: An article of importance in its field
Reviewer: Ulrich Lindemann

Reviewer's report:
This study describes an adequately designed intervention trial improving basic mobility in older persons with mild to moderate dementia. The manuscript is clearly written. The introduction follows a red line to the study aims. The methods are appropriately chosen and clearly described. The results are well-arranged presented and profitable discussed.

I have few suggestions which may help to (even) improve the manuscript.

Discretionary revision:
1. My major suggestion is to analyze more and different gait parameters. All the gait parameters you use are strongly associated with gait speed.

   Answer: We appreciate the constructive comment of the reviewer. As requested we have now additionally analyzed the gait parameters suggested by the reviewer (step time variability and Walk-Ratio, see comment 3 and 4 below). No significant improvements were found for these gait parameters after the intervention. We are discussing the limited intervention effects in the discussion section (page 16, line 4 - page 18, line 18)

2. Surprisingly, there seems to be no effect on step width, which must be discussed (!).

   Answer: Thank you for the comment. We have introduced a new section for discussing the limited effect on step width (page 16, line 7-20).

3. As you have correctly referenced in your introduction, gait variability (e.g. step time variability) is a relevant parameter and is not associated with gait speed. The GAITRite system has the potential to calculate this parameter.

   Answer: Based on the reviewer suggestion, we have now calculated this parameter and the results are displayed in Table 2. We have introduced a new section for discussing this parameter (page 18, line 19- page 19 line 7).

4. Furthermore, the Walk-Ratio (step length/cadence) seems to be an interesting parameter related to safe walking and easily to be calculated with your data.
**Answer:** Thank you for your suggestion. We have now calculated this parameter and the results are displayed in Table 2. We have introduced a new section for discussing this parameter (page 17, line 9-16).

5. If there wouldn’t be no effect on step width, you could report just on gait speed and your results were no stronger than other studies.

**Answer:** To address the reviewer’s concern, additional gait parameters (as suggested by the reviewer) have been calculated and are discussed in the manuscript (see comments above). We want to add to this comment that previous exercise trials in people with dementia have used mostly subjective or semi-objective (stopwatch) instruments which are observer dependent and do not provide spatio-temporal gait parameters (see statement in introduction). In contrast, the present study evaluates effects of a standardized progressive resistance and functional training using objective computerized gait analysis.

Minor essential revisions:

1. "Individuals were consecutively recruited." Please indicate the period of inclusion.

   **Answer:** The period of inclusion has been added to the manuscript (page 7, line 10). Thank you.

2. Did you really test the 1-RM during the intervention to adjust intensity or did you use the 10-RM in order to adjust weight increase? If you used the 10-RM, you should indicate.

   **Answer:** The 10-RM test was used in order to adjust intensity of resistance training during the intervention period. This is now indicated in the manuscript (page 8, line 10-11). The 1-RM has been used during the beginning and end of the study for quantification of intervention effects.

3. I would prefer consistent statistics (parametric or non-parametric) if possible for all calculations, but I leave this to the editor to decide.

   **Answer:** To address the reviewer’s request for using consistent statistics for all calculations, we are now using parametric statistics throughout the manuscript (depending on scale of the variable). A proper statistical test in now selected solely based on the scale of the investigated variable and not based on the observed distribution of the data. All variables except of ADL score and education (baseline comparison Table 1) were normally distributed. We have changed the following non-parametric statistics to parametric statistics:

   1) Baseline comparison Table 1. Barthel Activities of Daily Living score and education (years) are now presented as mean ± SD. Results between IG and CG are now compared by parametric test (t-test). The p-values remains nonsignificant (Barthel: P = 0.883; Education: P = 0.462) suggesting no significant between group differences at baseline.
2) Spearman correlations have been changed to Pearson’s r correlations. Results have been modified accordingly (page 13, line 13-19).

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
"I declare that I have no competing interests"