Author's response to reviews

Title: Effects of Cardiovascular Exercise Early After Stroke: A Meta-Analysis

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Version: 3 Date: 12 April 2012

Author's response to reviews: see over
Dear Arnold Bongcayao,

Please find enclosed a copy of the revised article we would like to offer *BMC Neurology* for review. We greatly appreciate the review of our Manuscript 1656240507653530. With this letter we would like to take the opportunity to respond to the reviewers’ comments and recommendations. Below we have listed the reviewers’ comments and recommendations in black. In blue writing we give our response to every single point brought forward.

Kindly note that we changed the title of the manuscript according to the journal’s guidelines to: “Effects of cardiovascular exercise early after stroke: systematic review and meta-analysis”.

We hope that this revision of the manuscript is now acceptable for publication in BMC Neurology.

Sincerely yours

Eling D. de Bruin
Reviewer number 1:

Discretionary Revisions

1. Throughout manuscript, suggest use of person-first language, e.g. individual with stroke, rather than stroke patient
2. Suggest referring to ‘person/participant’, rather than ‘patient’, since they are participants enrolled in research studies
3. Page 3 para 1: Replace ‘new stroke patients’ with ‘new cases of stroke’
4. Page 3 para 2: Remove ‘due to the traumatic event and’
5. Throughout manuscript, spell out number when beginning a sentence with a number. Some specific examples:
   a. Page 8 para 2: Replace ‘10 studies ...’ with ‘Ten studies ...’
   b. Page 9 para 4: Replace ‘2 studies ...’ with ‘Two studies ...’
6. Page 7 para 2: Delete ‘included’ in first sentence
7. Page 10 para 2: Replace ‘yield’ with ‘yielded’
8. Page 11 para 2: Replace ‘;’ with ‘:’
9. Page 16 para 2: Remove ‘However,’ from last sentence
10. Throughout manuscript, change ‘minor affected’ to ‘mildly affected’

Our answer (1-10): We implemented all your suggestions into the revised manuscript.

Minor Essential Revisions

1. Readers may have different perspectives on what is the ‘acute’ phase of stroke, so it would be helpful to clarify this. I suspect that the majority of the studies included in this meta-analysis refer to the sub-acute phase after stroke. That is, participants are medically stable and are participating in rehabilitation programs, and not in acute care settings. To avoid confusion, perhaps an operational definition would be helpful.

   Our answer: We adopted the comment of the reviewer and changed the definition in the manuscript as follows: For the purpose of this systematic review, the phase after stroke was defined by the start of the intervention, whereas we defined “acute” as the first week after the stroke event, and “sub-acute” as 7 days – 6 month after stroke onset. (Page 5 para 3)

2. The authors did note on page 9 para 1 that one study (which one? No reference was provided) did include a participant as early as 5 days post-stroke, but were they in acute care or rehabilitation?

   Our answer: We revised the “days post stroke” by showing only the data of the experimental groups. This led to a recalculation presented in Table 1 (Participants) and to a revision of our statement: The earliest time was 6 days post stroke. (Page 9 para 1)

   Regarding the setting, we stated previously that all studies were carried out during inpatient rehabilitation. (Page 8 para 2)

3. Correct units for VO2, should be ml/kg/min or ml#kg-1#min-1 (not ml/kg-1/min-1)

   Our answer: We implemented “ml/kg/min” throughout the manuscript.

4. Page 9 para 4: second sentence is redundant of data provided in Table 2

   Our answer: We deleted redundant information.
5. Page 12 para 1: VO2peak data was available in 3 studies, but authors cited 4 (references 35, 37, 42, 44). Please clarify this discrepancy.
   Our answer: Reference 35 (da Cunha 2002) does not belong to this group and is, therefore, excluded. (Page 10 para 1)

6. Page 14 para 1: specify which studies did not use same modalities for testing and training
   Our answer: This statement was excluded from the manuscript for clarity. (Page 13 para 4)

7. Page 15 para 4: Since there are many forms of bias, are the authors referring to potential intervention bias that may result from inconsistency of exercise protocols employed?
   Our answer: The paragraph was revised and now reads as: Various exercise protocols have been used to improve cardiovascular fitness. 3 studies used mixed training interventions [36, 37, 43] (strength, balance, endurance), and 2 studies did not explicitly exclude endurance training in the control group [35, 42, 45]. This inconsistent use of exercise protocols might lead to potential intervention bias regarding the evidence of optimal training protocols to be used in sub-acute stroke. (Page 15 para 4)

8. Page 17 para 2: The authors should acknowledge that the paucity of evidence regarding exercise testing and training among individuals with severe stroke is not unique to those in the early post-stroke phase, but is also a gap in knowledge in the later (chronic) stages after stroke.
   Our answer: The reviewer is most probably correct when he states that there is not only paucity of evidence regarding exercise testing and training among early stroke survivors, however, also in chronic stroke survivors. However, because we did not focus our review on chronic stroke survivors and we, therefore, did not stumble on this specific information, we are not able to credibly acknowledge this lack of information also in the chronic population. It is, furthermore, beyond the scope of our review to include this information. We just did not investigate this and can, therefore, not substantiate this acknowledgement. (Page 17 para 3)

**Major Compulsory Revisions**

1. Page 5 para 3 indicates ‘Participants of any age...’ but in the search strategy description earlier, studies including participants > age 18 years were included. Please clarify.
   Our answer: We appreciate the comment of the reviewer on this point. We have edited and clarified the text on page 5 para 3 to read: Participants (age >18 years) with initial stroke in the acute phase deemed medically stable enough to participate in an aerobic exercise intervention were considered.

2. The manuscript seemed disjointed in many places, and would benefit from some re-structuring for continuity and flow. For example:
   a. It would be helpful for the Methods to be mirrored in the Results, and to be consistent between these 2 sections.
      Our answer: Because we are following the PRISMA guidelines for reporting we ended up with the flow of information as presented in the first version of our manuscript. We acknowledge, however, the remark by the reviewer and partially agree. In the revision of the manuscript we try to be consistent and at the same time consider continuity and flow of the manuscript. We now neatly arranged between these 2 sections in the sense that the Methods now are mirrored in the results. We have revised the manuscript for continuity and flow.
b. Some sections in Results are missing from Methods, e.g. explanation for Risk of bias across studies.
Our answer: We inserted a separate chapter for “Risk of bias across studies”. This is to read as: We assessed the possibility of publication bias by evaluating funnel plots of the trials’ mean differences for asymmetry, which can result from non-publication of small trials with negative results. Heterogeneity of effect sizes was evaluated by $I^2$ statistics, where at least 50% was taken as an indicator of substantial heterogeneity. (Page 7 para 2)

c. In the Results, Synthesis of results (page 12) can be moved earlier, perhaps before Primary outcomes (page 10), as these are the main results of this meta-analysis and crux of the paper.
Our answer: We restructured the manuscript based on your comments and brought the synthesis of the results earlier. (Page 10 para 1)

d. On that note, what is difference between these 2 sections? Are VO2peak and 6MWT distance not the primary outcomes (as outlined on page 9 para 2)? Is gait speed not a secondary outcome, yet why was it reported in Synthesis of results along with VO2peak and 6MWT?
Our answer: Primary outcomes are directly related to aerobic capacity, whereas secondary outcomes represent all other used measures. Regarding the synthesis of the results, only VO2peak, 6MWT and 10MWT data allowed us to perform a meta-analysis, which resulted in an overall “Syntheses of results” chapter. However, our implementation of primary and secondary outcomes leads to confusions. We decided to exclude this terms and took the “Results of individual studies together”. (Page 10-11)

e. Page 10 para 2: Please report the ES, MD, 95%CI for change in VO2peak.
Our answer: The results were added to the manuscript and to read as: 3 studies reported between-group improvements in VO2peak after cardiovascular exercise (ES=0.90, MD=0.99, CI95%=0.54-1.44) [37], (ES=1.43, MD=4.99, CI95%=-1.18-11.16) [42], (ES=1.05, MD=0.60, CI95%=0.14-1.06) [44]. (Page 10 para 3)

f. Subsections on Risk of bias within studies and Risk of bias across studies could follow one another.
Our answer: Regarding the restructuring, it’s more clear to provide the risk of bias across studies after, and the risk of bias within studies before the syntheses of results. (Page 9-10)

3. Page 14 para 2 has some inconsistencies. At first, the authors refer to the ‘large effect size’ for VO2peak outcome, yet later attributed the short intervention lengths for the ‘small effects were to be expected’.
Our answer: We recognised potential for clarification in this part of the text. We actually referred to “small training effects”, and therefore changed and clarified the sentence into: However, the short intervention lengths (mean 6.56±3.7 weeks) that were used in the included trials may be indicative of the fact that only small training effects were to be expected. (Page 13 para 3)

4. Also on page 14 para 2, how did the authors conclude that individuals in the sub-acute phase of stroke have a larger potential for increasing VO2peak compared to chronic stroke?
Our answer: The reviewer is right with the identification of this seemingly inconsistency. We clarified this part of the text in the revised version. The comment is now redundant. The revised text reads: The results of the meta-analysis for the VO2peak outcome after cardiovascular exercise, in individuals starting exercise within 6 days to 6 months after stroke onset, revealed a
large effect size (SMD=0.83). This finding supports the evidence that individuals in the sub-acute stage after stroke have high potential to increase VO2peak following a cardiovascular training intervention. This is in addition to a spontaneous recovery of peak aerobic capacity of 16.9% that occurs during the first 6 months after stroke, as shown by MacKay-Lyons & Makrides [47]. (Page 13 para 3)

5. Page 14 para 2: The authors report that the ES for 6MWT distance was lower among studies that did not use walking training in the exercise intervention relative to studies that did, but this sub-analysis was not reported in the Results. Can the authors report the different ES for 6MWT distance among studies that did / did not utilize walking training as part of the intervention? Our answer: This is an important comment from the reviewer with which we agree. We have added different ES for 6MWT for studies that did / did not use walking training as major part of the intervention protocol in the manuscript. The revised text reads: Studies that used walking as a major part of the intervention protocol showed larger effect sizes in the 6MWT (ES=1.07, MD=34.90, CI95%=13.59-56.21) [38], (ES=1.89, MD=28.40, CI95%=9.81-46.99) [45] than studies that did not implement walking training (ES=0.67, MD=81.00, CI95%=68.00-230.00) [36], (ES=0.80, MD=28.02, CI95%=10.76-45.28) [37], (ES=0.67, MD=37.70, CI95%=-2.85-78.25) [44]. (Page 11 para 1)

6. Page 15 para 1 “… stair walking tests should last until fatigue”: It is possible that changes in stair climbing may be seen even without continuing until fatigue. Perhaps a timed test might still provide an indication of aerobic capacity (over a longer duration than climbing 1 flight of stairs). For example, a test that is analogous to the 6MWT (meant to reflect durations of daily functional activities but does not take the subject to the point of fatigue) might be appropriate and may still be responsive to change. The primary limitation is that no such test currently exists. Our answer: We agree. There is a lack of appropriate standardized tests to evaluate functional activities that are connected to aerobic capacity. We revised the section based on your suggestion. The revised text reads: What can be said is that if we are looking at aerobic capacity, stair-walking tests should have a longer duration than climbing 1 flight of stairs and reach symptom limited exhaustion of the participant. (Page 15 para 1)

7. From a practice standpoint, considering the potential impact of this manuscript on clinical practice, it is important for the readers to be fully aware of the procedures and protocols that were used in these studies to ensure participant safety. It would be helpful for the authors to provide some commentary or discussion in this regard. This will have important implications for knowledge translation, as health professionals who wish to implement exercise training for their clients may look to this research evidence to inform their practice. For example: Our answer: We inserted the chapter: “Clinical relevance” where we provide clear statements regarding the clinical implementation of our results. The text reads: Regarding the results of the present meta-analysis, cardiovascular exercise interventions and exercise testing protocols using leg cycle ergometry have been found to be safe and feasible in the sub-acute stage after stroke. There is robust evidence that individuals with sub-acute stroke may benefit from these protocols to improve peak oxygen uptake and walking distance. Therefore, cardiovascular exercise protocols should be implemented into sub-acute stroke rehabilitation since conventional physical therapy programmes between 2 and 14 weeks post stroke did not elicit adequate cardiovascular stress to induce a training effect [13]. Clinicians and researchers should follow ACSM guidelines for exercise testing and prescription to ensure medical safety of training protocols and comparability for future analyses. (Page 17 para 2)
8. Page 16 para 1: Can the authors provide more details regarding the screening procedures used by these studies to ensure safety of participants? Why were potential subjects excluded, e.g. unstable cardiovascular status or other reasons? Are these criteria different from standard criteria recommended by ACSM?

Our answer: We provided further information in the manuscript and refer to “Table 1”, that provides detailed information regarding inclusion- and exclusion criteria. The text reads: However, there were strict exclusion criteria in all studies, mostly based on the ACSM guidelines [46] (Table 1), thus individuals with stroke showing severe cardiac disease were not considered. Moreover, the applicability of cardiovascular exercise in the acute period after stroke (<7 days post event) remains unclear. (Page 15 para 5)

9. Page 16 para 2: It would be helpful to include some details on how the exercise tests were performed, specifically how the subjects were monitored for safety (HR, ECG etc) and what criteria for test termination were employed (if different from ACSM guidelines).

Our answer: We added extended information into the manuscript. (Page 12 para 2, Page 16 para 2)

10. Page 17 para 2: clarify what are ‘brain changes’, are the authors referring to cortical activation or re-organization? Or other structural or functional changes?

Our answer: We refer to structural re-organisation of the brain and clarified this point in the revised text. The revised text reads: It is well established that repetitions play a major role in structural re-organisation of the brain [56], and task-orientated activities are a key to functional recovery [57]. (Page 17 para 3)

11. Table 1: Why is the Time since stroke (days) ‘N/A’ for Katz-Leurer et al?

Our answer: We revised the “days post stroke” data (see point 2 in minor essential revisions). Katz-Leurer et al. only provides “>30 days post stroke”. (Table 1)

12. Overall, this paper would benefit from careful editing for grammar and language. Some specific examples:

Our answer: We implemented all your suggestions and edited the manuscript carefully for grammar and language by a native English speaker. In actual fact the last author of the manuscript is a British national who performed this part of the revision.

a. Page 3 para 1: Replace ‘population aged over 65’ with ‘population over the age of 65’

Our answer: Replaced. (Page 3 para 1)

b. Page 6 para 1: Replace ‘medically deemed stable’ to ‘deemed medically stable’

Our answer: Replaced. (Page 5 para 3)

c. Page 14 para 2: The sentence ‘Whether this is due to a lack of training intensity ...’ seems incomplete? Or, should the last word be ‘here’, rather than ‘where’?

Our answer: The last word should be “here”. This was a typing error. (Page 14 para 1)

d. Page 15 para 4: Unclear of intended meaning of ‘... falsify the outcomes regarding true effects ...’ Do they mean that the heterogeneity of the exercise protocols limits the clinical applicability? Or that we are left unclear of the optimal training protocol to be used in this population?
Our answer: We revised the paragraph. See also point 7 in minor essential revisions. (Page 15 para 4)

e. Page 17 para 1: ‘It is well known, e.g. …’ is an incomplete sentence
Our answer: We revised the sentence into: Fourth, reports of specific medication usage of the participants were not given in most studies; beta-blockers, for example, may affect cardiovascular responses during exercise [55]. (Page 17 para 1)

f. Page 17 para 2: ‘... these concepts are not feasible ...’ is not grammatically correct. Do the authors intend to convey that the findings are not applicable or relevant to individuals with severe functional limitations after stroke?
Our answer: We want to mention that patients with severe functional limitation are not able to perform exercise testing using leg cycle ergometry. The concept of exercise testing and the used cardiovascular exercise protocols are not applicable in severely affected individuals with stroke. We revised the paragraph accordingly. The text reads: Leg cycle ergometry or treadmill exercise has been shown to be adequate for moderately to mildly affected individuals with stroke, but these concepts are not applicable in severely affected individuals. (Page 17 para 3)

Reviewer number 2:

This is a methodologically sound meta-analysis of an area where data are limited to small numbers of patients which include both randomized and non-randomized studies and when the intervention has been undertaken in the non-acute phase following stroke. It clearly shows the limited numbers of patients recruited into the limited number of eligible studies (n=11, although 3 studies were from the same sample!) and is therefore able to draw some guarded conclusions regarding benefits of aerobic exercise following acute stroke. Of course there is inherent bias in terms of patient recruitment in only those individuals who presumably had minimal deficits and therefore the conclusions are not generalizable. The intervention in terms of type of exercise and frequency was comparable across studies. Primary outcomes were robust and included peak oxygen uptake (VO2peak), peak work rate (WRpeak), peak heart rate (HRpeak), heart rate variability, or the 6 Minute Walk Test (6MWT). Both VO2 and 6MWT do show consistent improvement.
Our answer: We hope to clearly describe the limitations of this meta-analysis in the revised version and to demonstrate clear directions for clinical applications and future research.