



# The Effects of High-Intensity Aerobic Exercise on Cognitive Performance After Stroke: A Pilot Randomised Controlled Trial

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## ABSTRACT

**BACKGROUND:** Aerobic exercise is an effective treatment to improve aerobic capacity following stroke and might also improve cognitive impairments in sub-acute stroke survivors. The aim of the study was to assess the effect of high-intensity aerobic exercise on cognitive impairments in sub-acute stroke survivors.

**METHODS:** A pilot, randomised controlled trial on the effects of aerobic exercise on cognitive impairments of stroke patients in the sub-acute (1-3 months) phase was conducted. Thirty patients with moderate cognitive impairments (maximum score of 5 on at least two items on the cognitive subscales of the Functional Independence Measure [FIM]) were included in the study and randomly assigned to either the intervention group – performing high-intensity aerobic exercise (above 70% of maximum heart rate), or the control group – performing low-intensity aerobic exercise (below 60%). Patients in both groups exercised for 50 min twice a week for 4 weeks. Primary neuropsychological outcome: Trail Making Test B.

**RESULTS:** Thirty stroke patients completed the interventions. The results showed that the high-intensity group, compared with the low-intensity group, achieved significant improvements on Trail Making Test B, which assesses processing speed and divided attention ( $P = .04$  after training and  $P = .01$  at follow-up). However, the significant improvements on Trail Making Test B might relate to a ceiling effect in the control group.

**CONCLUSIONS:** This study does not provide evidence to support that aerobic exercise can improve cognition in stroke survivors, even though significant improvement was revealed on the primary outcome in sub-acute stroke survivors following high-intensity aerobic exercise compared with low-intensity general exercise.

**KEYWORDS:** Sub-acute stroke survivors, moderate cognitive impairments, neuropsychological assessments, high-intensity training

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## Introduction

Aerobic fitness is acknowledged to improve aerobic capacity among healthy people. Aerobic capacity describes the functional capacity of the cardiorespiratory system (the heart, lungs, and blood vessels) and refers to the maximum amount of oxygen consumed by the body during intense exercises in a given time frame.<sup>1</sup> In recent years, there has been an increased focus on the relationship between physical activity and cognition<sup>2-5</sup> as well as aerobic fitness and stroke.<sup>6,7</sup> Furthermore, previous research on samples of elderly patients<sup>8,9</sup> and patients with mild cognitive impairment (MCI) indicates the potential benefits of intensive aerobic exercise in enhancing cognitive function.<sup>10</sup>

In Denmark (with approximately 5.5 million inhabitants),<sup>11</sup> the incidence of hospitalisation due to stroke is about 15 000 patients annually. About 50% of them need comprehensive neurorehabilitation.<sup>6</sup> The group of stroke patients is very heterogeneous. Age of onset is normally above 65, although 30% are below the age of 65.<sup>6,12</sup> These patients can have a wide

variety of impairments, which can affect physical, cognitive, emotional, and social functioning. Decline in cognitive function can hinder an effective rehabilitation process and have an impact on level of independence in daily activities and eventual return to work.<sup>13</sup> In the long term, cognitive impairments have been associated with increased costs of care<sup>14</sup> and increased risk of institutionalisation.<sup>15</sup> It has been argued that if cognitive impairments were independently associated with long-term outcomes and costs, this would lead to a shift towards a more enhanced focus on these impairments in stroke rehabilitation.<sup>16</sup>

In recent research, links between aerobic fitness and brain activity have been demonstrated.<sup>8,9,17,18</sup> Zoeller<sup>18</sup> found that exercise and greater aerobic fitness are associated with increased brain volume and a higher level of growth factors, which promote neurogenesis and angiogenesis. Holzschneider et al<sup>8</sup> found a positive association between cardiovascular fitness and changes in brain activation in the medial frontal gyrus and the cuneus in middle-aged men and women. A study including



older adults highlighted the neural changes in hippocampal areas due to physical exercise.<sup>19</sup> Increased physical activity may improve cognitive function, especially executive function in older adults.<sup>18</sup> In addition, several links between physical activity, cognitive functions, and stroke have been revealed.<sup>2</sup> Furthermore, physical exercise can be beneficial in treatment of MCI and dementia.<sup>10,20,21</sup> In a study including people with Alzheimer's disease, both physical activity and social aspects of group treatment seem to cause positive results.<sup>20</sup>

Physical activity and aerobic exercise are recommended as important components of a comprehensive stroke programme<sup>22,23</sup>; they can enhance aerobic capacity<sup>24</sup> and cognitive function.<sup>2</sup> In chronic stroke survivors, aerobic exercise appears to improve cognitive function.<sup>25-27</sup> However, few studies have addressed the effect of aerobic exercise on cognitive impairments in stroke survivors, especially including stroke survivors in the sub-acute phase. Two studies including sub-acute stroke survivors evaluated the effect of aerobic exercise, but did not include cognitive assessments.<sup>28,29</sup> Nevertheless, there is a great amount of literature demonstrating positive effects of aerobic exercise, including for people with other neurological diagnoses and the elderly.<sup>10,30-32</sup>

Studies investigating the effects of aerobic exercise on brain tissue volume,<sup>33</sup> angiogenesis,<sup>34</sup> and neurogenesis<sup>8</sup> have also shown positive effects. Unfortunately, many of these studies are limited by cross-sectional designs, for example, Holzschneider et al<sup>8</sup> or the use of animal subjects, for example, Luo et al.<sup>35</sup> In the studies including stroke survivors, a variety of modes and intensity of exercise are presented. Many of the studies do not solely perform aerobic exercise, but add strength training<sup>25</sup> or balance training,<sup>26</sup> and do not control for the effect of these variables.<sup>2</sup>

A recent meta-analysis of randomised controlled trial (RCT) evaluated the effects of aerobic exercise on cognition in patients following stroke.<sup>3</sup> Fourteen studies (736 participants) were included in the review. The study found a significant positive effect on cognition (attention/processing speed) of physical activity training post-stroke. However, the evidence of the effects of exercise on cognitive function after stroke is not all positive.<sup>24</sup> Other studies have shown mixed results, with improvements in some outcomes but not all. For example, Tang et al<sup>36</sup> did not see improvements with high- or low-intensity exercise; Oberlin et al<sup>3</sup> reported meta-analytic data to support improvements in attention and processing speed but not in executive function or working memory.

It is uncertain what exercise intensity level causes improvements in cognitive function (dose dependency). Moreover, in studies involving this patient group, the intensity of exercise is often either unspecified<sup>28</sup> or if described, the most common intensity is moderate.<sup>25,26</sup> Intensity levels of aerobic exercise are defined as<sup>37</sup> (a) high intensity: heart rate of 70% of maximum of heart rate as the lower limit and (b) low intensity: heart rate of 60% maximum of heart rate as the upper limit.<sup>37</sup>

Trials including older adults have shown that high intensity is beneficial compared with low intensity in improving aerobic capacity<sup>29</sup> and cognitive impairments.<sup>10</sup> Consequently, it might be hypothesised that performing high-intensity aerobic exercise also improves cognitive functions in stroke survivors. Based on recent studies of stroke survivors, it can be derived that in future research, the dose-response relationship between aerobic fitness and cognitive performance should be investigated and mode of exercise should be specified.<sup>25,38-40</sup>

The aim of the present study was to assess the treatment effect of high-intensity aerobic exercise on cognitive performance in stroke survivors in the sub-acute phase at an inpatient rehabilitation hospital. By improving aerobic capacity and cognitive functions in these patients, hopefully their rehabilitation outcome and future daily function will in turn be enhanced. One objective was to examine which level of intensity is required to obtain a potential effect, either high-intensity aerobic exercise or low-intensity exercise, or both or neither. Further objectives were to discover how procedures and measurements function in this setting and for this patient group.

Primary hypothesis:

- Divided attention and processing speed assessed by the Trail Making Test B improve more with high as compared with low-intensity physical exercise.

Secondary hypotheses:

- Cognitive performance on a broad range of neuropsychological tests that assess processing speed, attention, working memory, visual and verbal memory, and executive function improves more with high-intensity aerobic exercise compared with low-intensity physical exercise.
- Self-reported measures of affect (anxiety and depression) and impression of change improve more with high-intensity aerobic exercise compared with low-intensity physical exercise.
- Aerobic capacity and endurance improve more with high-intensity aerobic exercise compared with low-intensity physical exercise.

## Methods

### Research design

A RCT was employed to investigate the treatment effect of aerobic exercise and reported according to the CONSORT statements.<sup>41</sup> The intervention group performed aerobic exercise at a higher intensity and the control group performed physical exercise at a lower intensity. Including an active control group was important, to rule out the effect of extraneous variables, such as natural improvement and group effect.

**Table 1.** Selection criteria.

| INCLUSION CRITERIA   | EXCLUSION CRITERIA   |
|--|--|
| <ul style="list-style-type: none"> <li>• Sub-acute stroke (1-3 months after incident)</li> <li>• Age 20-70</li> <li>• Score of maximum 5 on at least two items on the cognitive subscales of FIM</li> <li>• A minimum score of 45 on Berg Balance Scale (BBS)</li> <li>• Length of hospitalisation expected to be &gt;4 weeks</li> </ul> | <ul style="list-style-type: none"> <li>• Medical conditions (e.g., heart or lung diseases) that would restrict participation</li> <li>• Not able to provide consent</li> <li>• Severe aphasia</li> <li>• Dementia or cognitive impairments diagnosis prior to stroke</li> <li>• Language barriers due to having a native language other than Danish</li> <li>• Enrolled in other projects</li> </ul> |

Abbreviation: FIM, Functional Independence Measure.

## Participants

Patients were recruited from three different neurorehabilitation wards at Hammel Neurorehabilitation and Research Centre (HNRC), a specialised neurorehabilitation hospital for rehabilitation of neurological patients focusing on acquired severe brain injury from Western Denmark and patients with moderate brain injury from the County of Aarhus. The patients were included if they met the inclusion criteria listed in Table 1.

To be included in the project, the patients had to have moderate cognitive impairments with a maximum score of 5 on at least two of the cognitive subcategories on the Functional Independence Measure (FIM). Furthermore, since the treatment was executed in a group setting, the participants had to be able to function socially and thus achieve a score of at least 3 on the social sub-score of FIM.

The physiotherapists on the wards were responsible for recruiting the participants. Another clinical physiotherapist randomised the patients into one of the two groups. Block randomisation of six was employed. Thirty-eight patients were recruited in total and 30 completed the intervention. Overall, mean age 53 (range: 22-67), see Table 4. Eight people did not complete intervention. Two excluded themselves due to a personal conflict with another participant. The participation of five people was fragmented due to competing diseases (e.g., flu) or injury (e.g., sprained ankle) and one was unexpectedly discharged due to family matters in the middle of the intervention, see Figure 1.

## Procedure

The frequency and duration of aerobic exercise were chosen based on clinical guidelines<sup>42</sup> and the clinicians' feedback. Both the experimental and control groups performed 4 weeks of exercise. Each group consisted of four to six participants. The frequency of twice-weekly training sessions was based on Danish guidelines, stating that this is sufficient to retain and improve endurance.<sup>42</sup> Exercise sessions were conducted in a fitness room on two fixed weekdays at a fixed time. Both groups exercised in the same room, at different timeslots (experimental group at 9-10 AM and control group at 10-11 AM) to minimise contamination bias. In rare cases, when patients had an urgent appointment on the exercise day, the exercise was moved to another time of the day or another day. During the study period, the participants were not doing alternative aerobic training.

After performing the 4 weeks of exercise and completing the study, both experimental and the control group were free to choose other forms of fitness training.

## Intervention Protocols

Trialling the procedures were performed before starting the project. Detailed programmes for the high- and low-intensity exercise groups were developed by two experienced physiotherapists, in cooperation with the researchers. Both programmes were tested in a small group of patients. The heart rate of each person in each group was measured to ensure that the two different programmes provided the intended difference in aerobic exercise intensity (Table 2). Throughout the 4-week intervention phase, the heart rate (beats per minute) of each participant was measured with short distance telemetry (Polar RS400).

Heart rate monitors with chest electrodes have proved valid and reliable when used during exercise.<sup>43</sup> One physiotherapist was responsible for adjusting personal details and pulse zones on each participant's pulse watch. The high-intensity group was to have a heart rate above 70% of maximum for at least 20 min during the session (Table 3). According to the American College of Sports Medicine (ACSM) guidelines, intensity above 70% of maximum heart rate for at least 20 min is necessary to expect an effect on aerobic capacity.<sup>37</sup>

The high-intensity exercise was performed in intervals of different durations with short breaks in between. An intensity of above 70% of maximum heart rate for a minimum of 20 min was ensured by the use of pulse zones, where the heart rate monitor gave a signal if the heart rate was too low.

The low-intensity group was to have a heart rate below 60% of maximum during the whole class. The exercise programme consisted of elements of balance, strengthening, and stretching. The intensity and duration of the strengthening exercises were low, and an effect on cognition was not expected.<sup>2</sup> All exercises were performed lying on a mat or in a sitting position. Pulse zones were adjusted for each participant, to make sure that they were below 60% of maximum heart rate.

Standardised programmes were used to ensure homogeneity of the performed exercise independent of the therapist leading the groups. This should contribute to increased reliability of the study. No restrictions of the patients' activity after finalising the aerobic fitness programme were included in the research design.

**Table 2.** Examples of heart rate monitoring: measured heart rate and percentage of maximum heart rate.

|  | HEART RATE MAX. | HEART RATE MIN. | AVERAGE HEART RATE | HEART RATE ZONE | TIME IN ZONE | TIME ABOVE ZONE | TIME BELOW ZONE |
|--|-----------------|-----------------|--------------------|-----------------|--------------|-----------------|-----------------|
| High-intensity exercise group (intervention) | 161 (90%)       | 104 (58%)       | 133 (75%)          | 120-146         | 31 min 40s   | 11 min 38s      | 10 min 39s      |
| Low-intensity exercise group (control)       | 114 (58%)       | 40 (20%)        | 84(42%)            | 99-119          | 5 min 6s     | 0 min 0s        | 41 min 11s      |

**Table 3.** High-intensity exercise session.

| TIME         | ACTIVITY   |
|--------------|--|
| <i>Time:</i> | <i>Ergometer cycle:</i>  |
| 5 min        | Warm up – moderate intensity 60%-70%   |
| 7 min        | High intensity above 70%   |
| 1 min        | Moderate intensity 60%-70%   |
| 7 min        | High intensity above 70%   |
| 2 min        | <i>Break</i>   |
| 10 min       | <i>Step – walk up and down</i> (for patients with balance difficulties, a bicycle was used instead): Could also be done as interval: 45 × 5 s with 45 s breaks |
| 10 min       | <i>Sit to stand from a low bench</i> (for patients with balance difficulties, a bicycle was used instead): 5 × 30s intervals with 45s breaks                   |
| 5 min        | <i>Cooling down</i> – either walking or cycling  |

Prior to study start, all involved clinicians (physiotherapists) and testers (physiotherapists and neuropsychologists) were trained in assessment and treatment procedures, in accordance with the project protocol. Making standardised programmes ensured that the aerobic exercise was performed as equally as possible, independent of the therapist leading the groups. This contributed to increasing the reliability of the study. Moreover, five physiotherapists shared the responsibility for leading the exercise sessions. Two were present at each session. The one who led the course and had the main responsibility was present as often as possible. The second therapist helped and guided the participants if needed. During the whole project, there was a close collaboration between the researcher and the clinical physiotherapists. Meetings were held frequently to discuss the challenges encountered.

### Assessments

Pilot trials of the physical and neuropsychological measurements were performed before study start. Assessments were made at baseline, after 4 weeks of intervention, and at 3-month follow-up. The participants were assessed within a week prior to starting the exercise and within a week following the intervention phase. To increase the reliability of the results, each patient was tested at the same time of the day and by the same assessor. All assessments were conducted by trained research staff members, internal or external, who were blinded to the allocation of patients.

The primary outcome measure was divided attention and processing speed, assessed by the Trail Making Test B.<sup>43</sup>

The secondary outcome measures included a standardised neuropsychological test battery, assessing the cognitive domains of processing speed, attention, working memory, visual and verbal memory, and executive function: Digit Span and Digit Symbol Coding from Wechsler Adult Intelligence Scale (WAIS-IV<sup>44</sup>; Trail Making Test A,<sup>45</sup> Serial subtractions [100-7],<sup>46</sup> Rey Complex Figure Test and Recognition Trial [RCFT],<sup>47,48</sup> Rey Auditory Verbal Learning Test [RAVLT],<sup>49</sup> Verbal Fluency Test,<sup>50</sup> and the Tower of London Test [TOL]).<sup>51</sup> Emotional outcomes were evaluated by self-reported questionnaires: the Anxiety (SCL-ANX4), Depression (SCL-DEP6), and Emotional Disorder (SCL-8) subscales from Symptom Check List 90-R (SCL-90).<sup>52</sup>

To evaluate the intervention effect on aerobic capacity and endurance, the Åstrand-Rhyming bicycle ergometer test<sup>37</sup> and the 6-min walk test (6MWT)<sup>53,54</sup> were employed. In addition, Patients' Global Impression of Change (PGIC) scale was performed after 4 weeks of intervention.<sup>55</sup> The patient's self-reported health condition has been shown to correspond well with change of physical and emotional functioning.<sup>56</sup>

### Statistical Analyses

The number of participants<sup>30</sup> was chosen after power calculation of a small testing group of 10 patients (five in each group). The MorePower tool was employed for this power calculation (Campbell and Thompson, 2012). The baseline characteristics are presented as medians and interquartile ranges for continuous data and as count and percentages for categorical data. Between-group comparisons (low- and high-intensity aerobic



**Table 4.** Participants.

| GROUP        | GENDER                           | AGE                                      | DIAGNOSIS   | MOTOR SYMPTOMS   |
|--------------|----------------------------------|--|---|--|
| Intervention | 7 Female (44%)<br>9 Male (56%)   | Median: 55<br>IQR: 50-60<br>Range: 43-67 | 13 Cerebrovascular accident (CVA) (81%)<br>3 Subarachnoid haemorrhage (SAH) (19%) | 8 Right side (50%)<br>6 Left side (38%)<br>2 Non (12%) |
| Control      | 9 Female (64%)<br>5 Male (36%)   | Median: 50<br>IQR: 44-56<br>Range: 22-64 | 8 CVA (57%)<br>6 SAH (43%)  | 2 Right side (14%)<br>8 Left side (57%)<br>4 Non (29%) |
|              | Fisher's exact test: $P = .2989$ | Wilcoxon's rank-sum test: $P = .1628$    | Fisher's exact test: $P = .2360$  | Fisher's exact test: $P = .0974$                       |

Abbreviation: IQR, interquartile range.

exercise) at baseline were done using the Wilcoxon rank-sum test for continuous data and Fisher's exact test for categorical data. The patients' self-reported impression of change (PGIC) was analysed by the Wilcoxon two-sample test.

A linear mixed model with random effect of subjects and systematic treatment effect was used to test for differences over time between the high- and low-intensity aerobic exercise groups. Post hoc analysis was conducted when the overall model showed statistically significant different time effects between groups to assess specific within-group and between-group treatment effects.

A 5% ( $P < .05$ ) statistical significance level was used throughout; however, to control for false positives due to multiple comparisons, the number of significant findings is compared with the probability of achieving this number of findings by chance. For example, the probability of one significant finding in 20 comparisons is 64% ( $P = .642$ ), two or more findings is 26% ( $P = .264$ ), three or more is 7.5% ( $P = .075$ ), four or more is 1.6% ( $P = .016$ ), and so forth.

All data were analysed using SAS/STAT software, version 9.4 for Windows, copyright© 2002-2012 by SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. There was missing data only for patient number 8. Due to unexpected hospital discharge, he completed only six sessions. Completer analysis was performed.

### Ethical Considerations

Ethical approval for this study was obtained by the Biomedical Research Ethics regional committee (1-16-02-182-12) and the Danish Data Protection Agency (journal no. 2012-58-006) and completed in accordance with the Helsinki Declaration 2008. The regional committee for Biomedical Research Ethics also approved the study. Written informed consent was obtained from all participants.

An information letter and a letter of consent were provided to the participants. The information letter was clearly written and verbal explanation was offered to ensure understanding of the project. The participants had 2 days to consider if they wanted to participate. Various ethical themes were considered,

for instance, all participants wore heart rate monitors to avoid uncomfortable situations such as over exhaustion.

### Results

From October 15, 2012 to September 15, 2015, 534 stroke patients were considered for inclusion in the project, but 474 did not meet the inclusion criteria because they were enrolled in other projects, were expected to be hospitalised for too short a period to complete the training course, or declined to participate. Thirty-eight eligible patients were included in the study, of which 19 were randomly assigned to high-intensity aerobic exercise training (intervention) and 19 to low-intensity aerobic exercise training (active control group). Eight patients disrupted the intervention for medical reasons, three in the intervention group, and five in the control group. The remaining 30 patients completed eight sessions of exercise over 4 weeks, 3-month follow-up testing and were included in the post-intervention analysis. All patients completed eight sessions of exercise over 4 weeks. All the participants achieved the targeted intensities as described in the protocol. Noticeably, although not statistically significant, it seems that more patients with right-side motor symptoms (left hemisphere stroke) was allocated to the intervention group (see Table 4).

The intervention group performed numerically worse on most measures at baseline (see Table 5), however significantly so only on Trail Making Test B.

### Physical Performances

#### *Aerobic fitness*

The baseline physical status ranges from low to very low in both the intervention group and the control group. The physical status at baseline, measured by fitness number, is generally lower within the intervention group but not statistical significant. Both groups improved numerically, the intervention group more than four points and the control group more than three points from baseline to immediate after intervention. The control group improved even further at 3-month follow-up, however not significantly more than the intervention group. No statistical significance between group treatment effects of aerobic fitness was revealed.

**Table 5.** Baseline, post-intervention, and 3-month follow-up for cognitive performance, aerobic fitness, and walking distance.

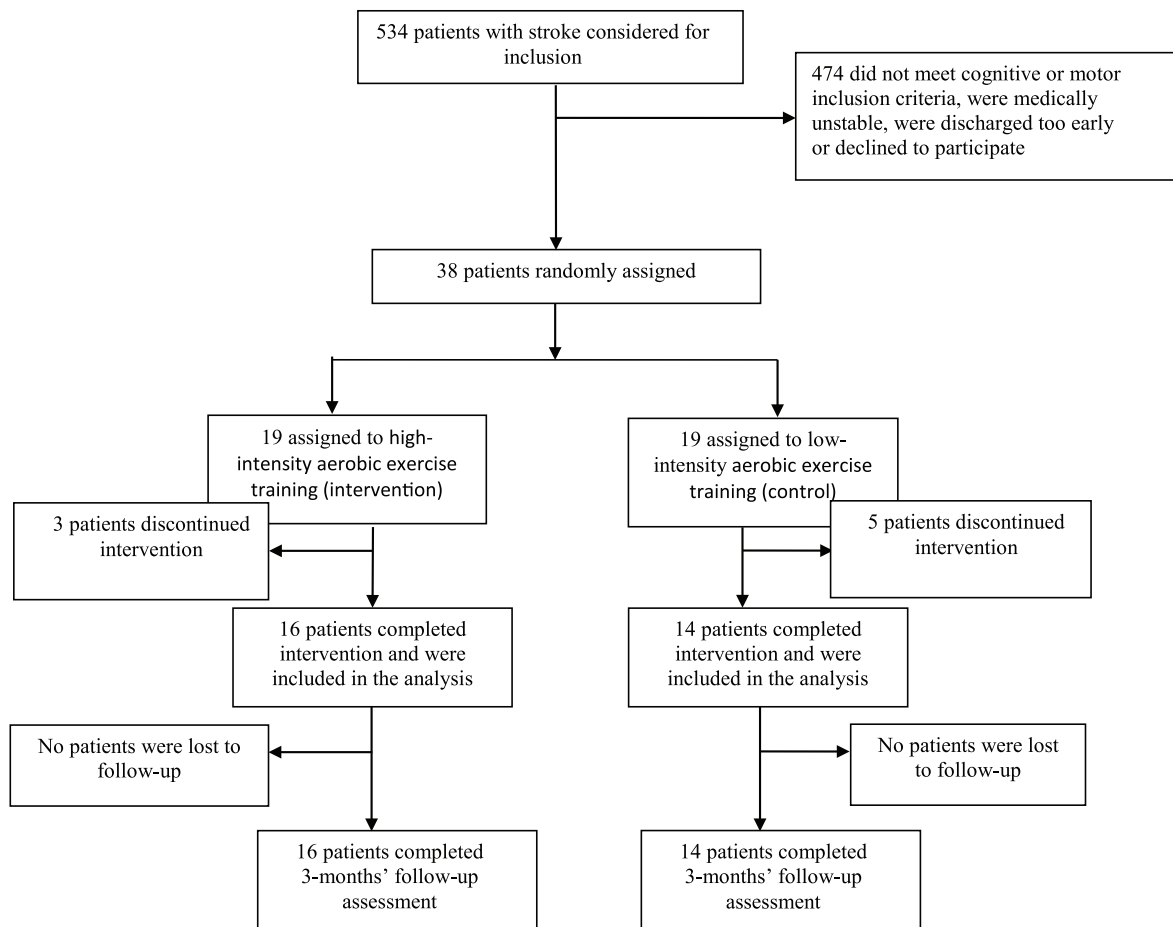
|   | GROUP 1 (INTERVENTION) |                    |                   | GROUP 2 (CONTROL) |                    |                   | P VALUE    |
|---|------------------------|--------------------|-------------------|-------------------|--------------------|-------------------|------------|
|   | BASELINE               | AFTER INTERVENTION | 3-MONTH FOLLOW-UP | BASELINE          | AFTER INTERVENTION | 3-MONTH FOLLOW-UP |            |
| Physical measurements   |                        |                    |                   |                   |                    |                   |            |
| Walking distance  | 520.75                 | 593.00             | 614.31            | 523.93            | 560.86             | 593.36            | .12        |
| Fitness number  | 28.12                  | 32.42              | 31.64             | 31.58             | 34.63              | 37.35             | .29        |
| Neuropsychological measurements processing speed  |                        |                    |                   |                   |                    |                   |            |
| Coding (WAIS-IV) raw score  | 42.80                  | 47.43              | 50.67             | 52.90             | 54.96              | 55.51             | .30        |
| Trail Making Test A   | 52.52                  | 40.22              | 38.63             | 36.81             | 33.58              | 31.91             | .26        |
| Trail Making Test B   | 141.14                 | 110.84             | 91.02             | 86.23             | 88.10              | 79.79             | <b>.02</b> |
| Working memory/attention  |                        |                    |                   |                   |                    |                   |            |
| Digit span (WAIS-IV) total raw score  | 19.78                  | 20.72              | 21.91             | 22.97             | 23.24              | 23.78             | .42        |
| Serial subtractions (100-7) seconds   | 74.57                  | 55.83              | 56.27             | 75.14             | 60.93              | 67.59             | .37        |
| Visual learning and memory  |                        |                    |                   |                   |                    |                   |            |
| RCFT copy time (s)  | 225.33                 | 188.35             | 188.72            | 216.20            | 182.20             | 171.38            | .89        |
| RCFT copy raw score   | 31.61                  | 32.00              | 31.00             | 31.63             | 30.27              | 31.01             | .27        |
| RCFT 3 min. recall score  | 15.69                  | 19.80              | 20.74             | 20.67             | 22.39              | 24.66             | .22        |
| Verbal learning and memory  |                        |                    |                   |                   |                    |                   |            |
| RAVLT learning total  | 32.99                  | 41.76              | 45.95             | 41.02             | 48.85              | 51.74             | .53        |
| RAVLT recall score  | 5.16                   | 6.52               | 7.36              | 8.16              | 9.93               | 10.10             | .60        |
| Executive function  |                        |                    |                   |                   |                    |                   |            |
| Verbal fluency (animals)  | 15.71                  | 17.34              | 18.35             | 21.13             | 23.13              | 22.68             | .65        |
| Verbal fluency (phonemic)   | 23.34                  | 26.28              | 28.41             | 27.17             | 34.02              | 34.11             | .36        |
| TOL movescore   | 25.89                  | 22.39              | 12.93             | 26.11             | 21.38              | 21.95             | .19        |
| TOL correct score   | 4.91                   | 5.20               | 6.75              | 5.13              | 5.10               | 4.85              | <b>.04</b> |
| TOL problem solving time  | 377.47                 | 325.11             | 257.58            | 326.86            | 272.26             | 304.57            | <b>.04</b> |
| Emotional reactions   |                        |                    |                   |                   |                    |                   |            |
| SCL-ANX   | 2.03                   | 1.47               | 1.05              | 1.06              | 1.35               | 1.36              | .31        |
| SCL-8   | 4.45                   | 3.10               | 2.87              | 2.81              | 2.18               | 3.01              | .52        |
| SCL-DEP   | 1.39                   | 0.90               | 1.25              | 0.83              | 0.82               | 1.43              | .59        |
| Patients' Global Impression of Change (PGIC) scale: Wilcoxon two-sample test: $P = .81$ . |                        |                    |                   |                   |                    |                   |            |

Three-month follow-up for Patients' Global of Change (PGIC) Scale. Results are presented by intervention and control group.  $P$  values are for group-time interaction.

Only 20 analysis variables are presented here. We made a total of 36 analysis variables, including partially scores. No correction has been made for multiple comparisons.

Abbreviations: PGIC, Patients' Global Impression of Change scale; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test and Recognition Trial; SCL, Symptom Checklist; TOL, Tower of London Test; WAIS-IV, Wechsler Adult Intelligence Scale IV.

## Results



**Figure 1.** Flow of patients through the trial.

### Mobility and speed

The 6-min walking distance test was similar at baseline in both groups. The intervention group improved on average by 73 m after intervention and the control group by 37 m. At 3-month follow-up, both groups had improved further; the intervention group another 21 m and the control 33 m; however, the group differences were not statistically significant.

### Cognitive function

No statistically significant group differences in cognitive performance were revealed at baseline, with the exception of divided attention and processing speed (Trail Making Test B), where the intervention group was significantly slower ( $P=.008$ ) before intervention. The average Trail Making Test B score of the intervention group revealed, in other words, significantly reduced performance at baseline, whereas the control group was close to the expected performance. A significant intervention effect could be shown on divided attention and processing speed (Trail Making Test B) immediately after the intervention ( $P=.04$ ) and at follow-up ( $P=.01$ ).

A significant post-intervention effect was found on executive functions (TOL correct score and solving time) at follow-up ( $P=.04$  and  $P=.04$ ). However, the remaining neuropsychological domains did not reveal significant intervention effects, although numerical improvements were evident in both groups. With respect to patients' self-reported impression of change (PGIC), there was no significant difference between the groups after intervention ( $P=.81$ ).

### Discussion and Limitations

Our hypothesis that high-intensity exercise training would be superior to low-intensity exercise training in improving cognitive impairments was not confirmed. The results did show that the high-intensity group, compared with the low-intensity group, had a significant intervention and post-intervention effect on Trail Making Test B (primary outcome), which assesses processing speed and divided attention ( $P=.002$ ), and a post-intervention effect on TOL, which assesses executive functioning, total correct score ( $P=.04$ ) and problem solving time ( $P=.04$ ).

However, for several different reasons, we conclude that these results are most likely not true intervention effects. First

of all, we found a ceiling effect on the primary outcome measure at baseline. The intervention and control groups differed significantly on Trail Making Test B at baseline level; the intervention group revealed significantly reduced performance, whereas the control group had close to expected performance. This inequality left less room for intervention effects in the control group, as improvement beyond the age-expected norm would be highly remarkable. Likewise, Quaney et al<sup>38</sup> used Trail Making Test in a similar RCT study (70% of heart rate, 45 min, three sessions a week for 8 weeks) of 38 participants and no significant difference between aerobic exercise and usual physical activity was revealed.

Second, we found a randomisation skew. A notable group difference at baseline is that more patients in the intervention group had right motor impairments (left side stroke), possibly affecting the performance of their dominant hand in neuropsychological tests requiring fine motor skills as well as verbal performance.

Furthermore, post-intervention effects on TOL are hard to justify theoretically. One would expect an intervention effect to be evident immediately after the intervention had ended, and that it would, hopefully, last long enough to be quantifiable at 3-month follow-up, but the converse was found in the present study.

All the participants got some kind of medications (standard care after stroke) which may play an important role in recovery process including cognitive functions. Unfortunately, the protocol contained no record of medications. In a subsequent study, it would be relevant to investigate how medications affect aerobic training.

Finally, there were multiple comparisons and the risk of false positives. Three statistically significant findings, of which two were observed post-intervention, in a total of 20 comparisons are not more than one would expect from sheer coincidence ( $P = .075$ ). In other words, the risk of false positives (type 1 error) is high.

There are several possible reasons as to why it might be difficult to show intervention effects of aerobic exercise among sub-acute stroke survivors compared with other patient groups. One possible reason might concern intensity of aerobic exercise and difference of intensity between the groups: there might be a true change in cognition, but the intensity of aerobic exercise was too small to reveal it. The intervention groups did not differ significantly on the effect of aerobic exercise on aerobic capacity (proximal outcome). It is hard to imagine the intervention effect to transfer to cognitive performance (distal outcome). Likewise, the systematic review by Cumming et al<sup>2</sup> found some evidence that increased physical activity enhanced cognitive performance. However, they also found notable limitations concerning considerable variance in terms of type and intensity of physical activity (aerobic training, resistance training, and usual physical activity). Future studies should take action to ensure that the intensity of aerobic exercise is high

enough and differs enough between groups to detect a difference on aerobic capacity before moving on to transfer effects. A further consideration is whether frequency and duration of exercise should be taken into account.

Furthermore, a third arm in the RCT design, where a control group only received ordinary therapy (treatment as usual), could have eliminated this factor. Including a stratified randomisation procedure could make sure that participants in the experimental groups have similar cognitive performance at baseline.

Another possible reason why it might be difficult to show intervention effects is statistical power. In other words, there might be an effect on cognition, but the groups are too small to detect it. However, achieving high numbers was not possible due to limitations in resources and time. For instance, length of stay has been reduced in recent years. In addition, it is not always possible to perform neurophysiological and neuropsychological testing in the first weeks following stroke due to cognitive instability in the acute phase. Future studies could be trans-sectional, so the intervention would begin while the patients are still hospitalised and continue in the municipalities after discharge. However, achieving a high enough number of sub-acute stroke survivors could turn out to be difficult. The challenge of recruiting a uniform group of individuals has also been pointed out in a recent systematic review.<sup>57</sup> Another possibility is a multicentre study, where a sufficient number of participants can be included within a reasonable time frame.

An additional reason of the lack of treatment effect could be spontaneous remission: there might in fact be a true treatment effect on cognition, but this effect competes with spontaneous remission and treatment as usual; hence, it is difficult to get significant results. The idea of detailed programmes for the high- and low-intensity exercise groups seems appropriate; nevertheless, the difference between the two groups was too small.

Sensitivity of outcome measures might as well be questioned. There *might be* a treatment effect on cognition, but the measures are not sensitive enough to capture the change. The tests were chosen by a neuropsychologist based on previous studies and clinical experience. All neuropsychological measurements were performed sitting at the desk and it is questionable to what degree these tests are sensitive to changes in the cognitive impairments as a result of aerobic exercise. Furthermore, after finalising the data and power calculations, we found that several of the included cognitive measurements needed a very high number of participants and therefore would be difficult to achieve.

The relevance of discussing outcome measures seems likely for other reasons too. There might not be an effect on cognition, but may be in other and more functionally relevant outcome measures that combine motor and procedural activity of daily living (ADL) skills, such as the Assessment of Motor and Process Skills (AMPS).<sup>58</sup> Including measurement in daily



activities might have been more sensitive in detecting possible changes in cognitive performance in this group of stroke survivors. Another measurement which could have been employed is the ADL-focused occupation-based neurobehavioral evaluation (A-ONE).<sup>59</sup> This instrument could evaluate the performance of activities of daily living and neurobehavioral impairments that would influence the performance. One challenge with the applicability of both instruments to the clinical setting is that the therapist conducting the measurements would need several training sessions.<sup>60</sup>

Finally, we must be critical of the aetiology of participants. There might *not* be a treatment effect of aerobic exercise on cognition among stroke survivors, but maybe only on older patients and patients with dementia, as previously documented by Larson et al.<sup>31</sup> It is one thing to improve cognitive deficits following acquired brain injury; it is another thing to slow down cognitive decline (cognitive reserve) due to ageing or neurodegenerative disease.

However, it is interesting to note that the control group appeared to have improved from post-intervention to 3-month follow-up with respect to aerobic fitness and mobility and speed compared with the intervention group (see Table 3). We hypothesise that this might have occurred because many of the control participants described at follow-up that they enjoyed the group interaction and having to exercise at maximum. Many of the control participants reported having started high-intensity aerobic exercise in a community centre post-discharge.

Although this study is small and did not show effects of aerobic exercise on cognition, it provides several important clinical implications. Performing cardiorespiratory exercise can prevent reduced physical function, disability,<sup>24</sup> medical sequelae, and cognitive deterioration, which are often seen in chronic stroke patients and of an advanced age.<sup>61,62</sup> Exercising at a high intensity was safe for this group of sub-acute stroke survivors when heart rate monitoring was performed. Moreover, the exercise is feasible and does not demand a lot of technical equipment or staff training and could therefore be employed in clinical practice in a hospital setting. Due to the limited duration of hospital stay, the treatment initiated is essential to achieve the best possible outcome for future community rehabilitation. The results from this pilot study may have implications for clinical practice in early rehabilitation in hospitals. Studies including stroke survivors in a sub-acute phase have not examined cognitive effects. The pilot study also demonstrated that it is possible for this patient group to complete high-intensity exercise for a period of 4 weeks with no adverse reactions. Aerobic exercise is thus safe and possible to perform for stroke patients with moderate cognitive impairments. It is also important that the treatment can be transferred easily to the community setting. The exercises performed in this study are applicable both to inpatient therapy and in the community post-discharge.

Finally, limitations of previous studies have been the use of variable exercise programmes and lack of descriptions of exercise, which makes replicability in clinical practice difficult. For this pilot study, standardised protocols were used and intensities were measured. These methodological strengths make replicability easier.

## Conclusions

In conclusion, even though significant improvement was revealed on the primary outcome in sub-acute stroke survivors following high-intensity aerobic exercise compared with low-intensity general exercise, this study do not provide sufficient evidence to support that aerobic exercise can improve cognition in stroke survivors.

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## Author Contributions

HP, MB, ARP, JFN, and LE wrote the manuscript. HP, MB, ARP, and JFN developed the concept and design of the study. HP and MB were involved in data collection. ARP conducted the statistical analysis. All authors were involved in the interpretation of the results and critically appraised the manuscript. All authors have read and acknowledged the final manuscript.

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