Using Aerobic Exercise to Improve Health Outcomes and Quality of Life in Stroke: Evidence-Based Exercise Prescription Recommendations

Marco Y.C. Pang, Sarah A. Charlesworth, Ricky W.K. Lau, Raymond C.K. Chung

Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong, SAR, China; Cardiovascular Physiology and Rehabilitation Laboratory, Physical Activity Promotion and Chronic Disease Prevention Unit, University of British Columbia, Vancouver, B.C., Canada

Results: Twenty-five trials fulfilled the selection criteria, of which 8 were level 1 studies. Treadmill and cycle ergometer were the two most popular modalities used to provide aerobic training. The most commonly adopted exercise session duration and frequency was 21–40 min and 3–5 days per week, respectively. The duration of the training programme varied, ranging from 3 weeks to 6 months. Over 60% of the trials used a high training intensity (60–80% heart rate reserve). Meta-analysis showed a significant effect on peak oxygen consumption, peak workload, maximal gait speed and walking endurance in favour of aerobic exercise. Meta-analysis revealed no significant effect on self-selected gait speed, Berg balance score and Functional Independence Measure score. The efficacy of aerobic exercise in improving other health outcomes in physical, psychosocial and cognitive domains as well as quality of life was inconclusive. The health risk associated with engaging in such exercise is small.

Conclusions: There is strong evidence that aerobic exercise (40–50% HRR progressing to 60–80%) conducted 20–40 min and 3–5 days per week is beneficial for enhancing aerobic fitness, walking speed and walking endurance in people who have had mild to moderate stroke and are deemed to have low cardiovascular risk with exercise after proper screening assessments (grade A recommendation). The effects of aerobic exercise on other health outcomes require further study.

Key Words
Cerebrovascular accident · Physical activity · Cardiovascular · Stroke · Exercise training

Abstract
Background: Stroke patients often suffer from poor cardiovascular health and deficits in physical, psychosocial and cognitive functioning. Aerobic exercise training may be a viable treatment approach to address these health issues. The objective of this systematic review was to determine the effects of aerobic exercise on various indicators of health, functioning and quality of life in stroke patients. It was hypothesized that the systematic review would reveal compelling support for the effectiveness of aerobic exercise in stroke patients, such that detailed evidence-based exercise prescription recommendations could be derived.

Methods: Major electronic databases were searched systematically to identify randomized controlled studies that examined the effects of aerobic exercise in stroke patients (last search performed in January 2012). The methodological quality of each study was evaluated using the PEDro scale (9–10 = excellent; 6–8 = good; 4–5 = fair; <4 = poor). Based on the methodological quality and sample size used, the level of evidence was determined for each study (level 1: PEDro ≥6 and sample size >50; level 2: PEDro ≤5 or sample size ≤50). Meta-analysis was performed on a given outcome when appropriate.

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Introduction

Stroke is one of the most common disabling conditions worldwide. The various physical impairments that ensue from stroke may further encourage a physically inactive lifestyle [1]. The lack of physical activity may trigger a vicious cycle of poor cardiovascular fitness, increased risk of cardiovascular disease, deterioration of physical functioning, and ultimately reduced quality of life. It is well documented that the risk of recurrent stroke and major cardiovascular events is particularly high in this patient population [2–5]. Cardiovascular fitness in individuals with stroke, which is often reflected by the peak oxygen consumption rate (peak VO$_2$), has also been found to be as low as 50–80% of the age- and sex-matched values in inactive individuals [6–7]. Poor cardiovascular fitness has been related to reduced ambulatory capacity in individuals with stroke [8, 9]. In fact, the aerobic fitness level of many stroke survivors does not even reach the critical value that is essential for independent living [10].

Aerobic exercise training may have an important role in improving cardiovascular fitness and other health outcomes among stroke patients by breaking the vicious cycle of physical inactivity and functional decline, and has gained increasing attention from clinicians and researchers in the past decade. The objective of this systematic review was to examine the effect of aerobic exercise on aerobic fitness and health indicators in cardiovascular, psychosocial and cognitive domains, functional ability and quality of life in people with stroke. We also aimed to develop evidence-based exercise prescription recommendations based on these analyses. We hypothesized that the systematic review of the literature would reveal compelling support for the effectiveness of aerobic exercise in people with stroke, such that detailed evidence-based exercise prescription recommendations could be derived.

Methods

The PICO method [11] was used to define the four major components of the systematic review question: P (patient) = patients with stroke; I (intervention) = exercise programmes that include a substantial aerobic exercise component, with aerobic exercise being defined as a structured exercise programme that involves the use of large muscle groups for extended periods of time in activities that are rhythmic in nature, including but not limited to walking, stepping, running, swimming, cycling and rowing [12]; C (comparison) = no intervention or other activities not designed to improve aerobic fitness; O (outcome) = aerobic fitness and other health indicators in cardiovascular, psychosocial and cognitive domains, functional ability and quality of life.

The eligibility criteria for article selection were formulated on the basis of the preceding study question. The inclusion criteria were: randomized controlled trials (RCT) that investigated the effects of aerobic exercise in stroke patients; that the aerobic training protocol was clearly described (e.g. intensity), and that studies were published in English. The exclusion criteria were: studies that used electrical nerve or muscle stimulation as the exercise protocol because the pattern of motor unit recruitment induced by electrical stimulation is very different from that in voluntary movements [13]; reports published in books; doctoral dissertations or reports published in conference proceedings. In this review, acute, subacute and chronic stroke were defined as 0–1, 1–6 and >6 months after the onset of stroke, respectively.

The primary outcome of interest was aerobic fitness, which is indicated by peak VO$_2$ achieved during a graded exercise test on a cycle ergometer or treadmill [12]. Peak workload and peak heart rate were also included in the analysis due to its direct relationship with peak VO$_2$ [12].

In addition, other indicators of general health status, particularly those relevant to cardiovascular health, were also of interest and considered as secondary outcomes in this systematic review. These outcomes included body composition, body weight, Body Mass Index, body composition, waist girth, resting heart rate and blood pressure, blood lipid profile, glucose tolerance, insulin sensitivity, leg blood flow, cerebral vasomotor reactivity and cardiac risk factors.

Whether aerobic training can lead to improvement in other relevant outcomes that are of main interest to clinicians (e.g. functional ability, psychological health, cognitive function and quality of life) is an important research question. Thus, these outcomes were also examined in this systematic review.

The following electronic databases were searched online through the local university’s library system by a research team member: MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica database (EMBASE), SPORTDiscus and PsychINFO. The specific search strategy for the MEDLINE database is described in online supplementary appendix 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000346075). A similar search strategy was used for other databases. The Cochrane Library Database of Systematic Reviews and Physiotherapy Evidence Database (PEDro) [14] were also searched online, with the last search performed in October, 2011. For these databases, the keyword ‘stroke’ was used for the search. The titles and abstracts of the articles generated by the search strategy were first screened to eliminate irrelevant articles. For the remaining papers, the full text was reviewed to determine eligibility. The reference list of each selected article was checked to identify other potential articles. A forward search was also performed using the Science Citation Index in January 2012 to identify all relevant articles that referenced the selected articles.

The PEDro score of each selected study, which is an indicator of the methodological quality (9–10 = excellent; 6–8 = good; 4–5 = fair; <4 = poor), was identified by searching the PEDro website (table 1) [15]. The PEDro scale is a common tool used to assess the scientific rigor of experimental studies and has been shown to be a more comprehensive measure of methodological quality than the Jadad scale in stroke rehabilitation literature [15]. Based on the PEDro assessment and sample size used, the level of evidence was assigned to each study. High-quality RCTs (rated as good or ex-
Excellent by PEDro and sample size \( \leq 50 \) were considered level 1 evidence, whereas lower-quality RCTs were considered level 2 evidence (rated as fair or poor by PEDro, or sample size \( > 50 \)) [16–18]. The article selection and data extraction were performed by two research team members independently. The results were then confirmed by the principal investigator.

Meta-analysis was conducted when appropriate to estimate the pooled treatment effect using Review Manager (version 5.1, The Nordic Cochrane Center, Copenhagen, Denmark). Prior to meta-analysis, the possibility of publication bias was first assessed using Egger’s regression asymmetry test [19]. This analysis was based on a regression model in which the standard normal deviate was regressed against the study-specific estimate of the precision of effect size. When no publication bias was present, the points would scatter around a regression line that ran through the origin. Publication bias was considered to be present if the intercept of the Egger’s regression line deviated from zero with a two-sided \( p \) value \( < 0.10 \) [19]. Meta-analysis was performed only if five or more studies measured the same outcome of interest, and no significant publication bias was found.

The change score (post-intervention score – pre-intervention score) and baseline standard deviation (SD) for each of the ex-

#### Table 1. Summary: methodological quality of studies and stroke characteristics

<table>
<thead>
<tr>
<th>Methodological quality</th>
<th>Studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEDro rating criteria</td>
<td></td>
<td></td>
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<tr>
<td>Eligibility criteria specified(^1)</td>
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<td>25–44, 48–54</td>
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<tr>
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<td>24–54</td>
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<tr>
<td>Concealed allocation</td>
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<td>26, 29, 31, 33, 40–42, 45, 48, 50, 54</td>
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<tr>
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<td>24, 26–54</td>
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</tr>
<tr>
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<td>0</td>
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<tr>
<td>Assessor blinding</td>
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<td>26–33, 37, 41–45</td>
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<tr>
<td>Less than 15% dropouts</td>
<td>16</td>
<td>27–31, 33, 37, 39–42, 44, 45, 49, 52–54</td>
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<tr>
<td>Intent-to-treat analysis</td>
<td>13</td>
<td>26, 29, 31, 33, 38, 40–42, 45, 49, 50, 53–54</td>
</tr>
<tr>
<td>Between groups statistics reported</td>
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<td>24–54</td>
</tr>
<tr>
<td>Point estimates and variability data reported</td>
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<td>24–54</td>
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<tr>
<td>PEDro total score</td>
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<td></td>
</tr>
<tr>
<td>Excellent (9–10)</td>
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<td>0</td>
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<tr>
<td>Good (6–8)</td>
<td>16</td>
<td>26–31, 33, 37, 40–42, 44, 45, 49, 50, 53, 54</td>
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<tr>
<td>Fair (4–5)</td>
<td>8</td>
<td>24, 32, 38, 39, 43, 48, 51, 52</td>
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<tr>
<td>Poor (0–3)</td>
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<td>25</td>
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<td>Sample size</td>
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<td></td>
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<tr>
<td>( \leq 50 ) subjects</td>
<td>12</td>
<td>24, 25, 30, 31, 37, 44, 48–50, 52–54</td>
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<td>26–29, 32, 33–36, 38–43, 45, 51</td>
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<tr>
<td>Level of evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>8</td>
<td>26–29, 33, 40–42, 45</td>
</tr>
</tbody>
</table>

| Stroke characteristics                        |         |            |
| Stage of stroke recovery                      |         |            |
| Acute                                        | 4       | 27, 39, 49, 53 |
| Subacute                                     | 2       | 29, 37     |
| Chronic                                      | 13      | 24, 25, 30, 32, 33, 38, 42–44, 48, 51, 52, 54 |
| Acute + subacute                             | 3       | 31, 45, 50 |
| Subacute + chronic                           | 2       | 40, 41     |
| Acute + subacute + chronic                   | 1       | 26         |
| Stroke type                                  |         |            |
| Ischemic only                                | 12      | 31, 32, 37–39, 42–44, 51–54 |
| Haemorrhagic only                            | 0       | 0          |
| Ischemic + haemorrhagic                      | 9       | 27, 29, 30, 33, 40, 41, 45, 48, 49 |
| Not reported                                 | 4       | 24–26, 50  |

\(^1\) This item is rated as ‘Yes’ or ‘No’, and is not used for calculation of the total PEDro score.
Experimental and control groups were used for the meta-analysis [20–22]. The SD of change score was not used as it may lead to inflation of effect size [20–22]. The degree of heterogeneity was assessed by the I^2 test for each outcome. Non-significance of the I^2 test implies that the results of different studies were similar (p > 0.05) and a fixed effects model was used. Otherwise, a random-effect model was applied. The size of the pooled treatment effect was defined as small (0.2–0.5), medium (0.5–0.8) or large (≥0.8) [23].

Further analyses were done to examine the relationship between the various parameters of the training protocols and the effect sizes obtained. As the criteria for parametric statistics were not fulfilled, non-parametric Mann-Whitney U test was used to compare the standardized mean difference (SMD) scores of peak VO_2 and other outcomes between studies that used different training modalities (cycle ergometer vs. treadmill). Spearman’s rank coefficient was used to examine the relationship between the SMD scores and training frequency and duration.

In addition, a grade of recommendation was determined for the use of aerobic exercise in improving each outcome of interest: grade A, strong recommendation = benefits clearly outweigh the risks, evidence is at level 1, 2 or 3; grade B, intermediate recommendation = unclear if benefits outweigh risks, evidence is at level 1, 2 or 3; grade C, weak recommendation, is based on level 3 or 4 evidence and is thus irrelevant to this review [16, 17].

Results

A total of 11,539 articles were generated from the aforementioned search strategy after removing the duplicates (fig. 1). Sixty-seven articles were eliminated after reading the full text (online suppl. appendix 2). Thirty-one articles fulfilled all criteria and were selected for this review [24–54]. Of these, Katz-Leurer et al. [27, 28], Pang et al. [33–35], Eng et al. [36] and Langhammer et al. [45–47] reported different outcomes in separate articles. In summary, a total of 25 trials were included in this review.

Considering both the PEDro ratings and sample size used, eight studies provided level 1 evidence [26–29, 33–36, 40–42, 45], whereas the others were considered level 2 studies (table 1). Over 50% of the trials only studied chronic stroke patients (table 1). In most of the selected studies, the stroke patients had sustained mild or moderate deficits in motor function and functional abilities (online suppl. appendix 3). Individuals with significant cardiovascular conditions (e.g. uncontrolled hypertension, peripheral vascular diseases, etc.) were not enrolled (online suppl. appendix 3).
Treadmill and cycle ergometer were the two most popular modalities used to provide aerobic exercise training (Table 2). The most common exercise frequency and duration used was 3–5 days per week and 21–30 min per day, respectively. More than 60% of the trials used a high training intensity [60–84% heart rate reserve (HRR), 77–93% maximal heart rate] [24, 27, 30, 32, 33, 38–40, 42–44, 48, 50–52, 54]. The details of the treatment protocols and outcomes are provided in online suppl. appendix 4.

<table>
<thead>
<tr>
<th>Modality used for aerobic exercise</th>
<th>Studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle ergometer</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Treadmill</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Exercise in water</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cycle ergometer + treadmill + arm ergometer/stepper</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Mixed (functional training, treadmill, cycling)</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>

Aerobic exercise time per session, min

<table>
<thead>
<tr>
<th>Tally</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>1–10</td>
<td>0</td>
</tr>
<tr>
<td>11–20</td>
<td>0</td>
</tr>
<tr>
<td>21–30</td>
<td>0</td>
</tr>
<tr>
<td>31–40</td>
<td>0</td>
</tr>
<tr>
<td>41–50</td>
<td>0</td>
</tr>
<tr>
<td>51–60</td>
<td>0</td>
</tr>
<tr>
<td>&gt;60</td>
<td>0</td>
</tr>
</tbody>
</table>

Aerobic exercise intensity

<table>
<thead>
<tr>
<th>Tally</th>
<th>Low (20–39% HRR, 50–63% HRmax)</th>
<th>1</th>
<th>4</th>
<th>37</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate (40–59% HRR, 64–76% HRmax)</td>
<td>7</td>
<td>28</td>
<td>25, 32, 38, 41, 45, 49, 53</td>
</tr>
<tr>
<td></td>
<td>High (60–84% HRR, 77–93% HRmax)</td>
<td>16</td>
<td>64</td>
<td>241, 27, 30, 32, 33, 38, 40, 42–44, 48, 50–52, 54</td>
</tr>
</tbody>
</table>

Interval type

| Tally | (periods of high intensity interspersed with low intensity) | 1 | 4 | 29 |

HRmax = Maximal heart rate.

1 Average number of steps taken was 3,896 steps per session.
2 Target intensity was described as ‘highest level attainable by the subject’.
3 Target intensity was set using the rate of perceived exertion of 13–16 according to the Borg scale.

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**Primary Outcomes**

**Aerobic Fitness**

In our primary meta-analysis incorporating all 15 trials that measured peak VO₂, a significant beneficial effect of the aerobic exercise was found (SMD = 0.55, p < 0.001; fig. 2a). Significant treatment effect was also found in various sensitivity analyses by including only: (1) aerobic trials with better methodological quality (PEDro score ≥ 5; SMD = 0.58, p < 0.001; fig. 2b), (2) chronic stroke aerobic exercise.
Potempa, 1995 [24] 2.2 4.36 19 0.1 4.79 23 6.5 0.45 (–0.17, 1.06)
Duncan, 2003 [29] 1.05 3.3 44 0.06 2.9 48 14.5 0.32 (–0.09, 0.73)
Chu, 2004 [30] 3.9 3 7 0.5 3.2 5 1.6 1.02 (–0.23, 2.27)
Macko, 2005 [32] 2.4 5.1 32 0.2 5.4 29 9.5 0.41 (–0.09, 0.92)
Pang, 2005 [7] 2 5.2 32 0.3 4.3 31 9.9 0.35 (–0.15, 0.85)
Ivey, 2007 [38] 2 4.59 26 –0.4 4.02 20 6.9 0.54 (–0.05, 1.14)
Lennon, 2008 [42] 1.4 1.6 23 0 1.8 23 6.7 0.81 (0.20, 1.41)
Luft, 2008 [43] 2.3 4.34 37 –0.4 4.46 34 10.8 0.61 (0.13, 1.08)
Lee, 2008 [41] 1.85 3.86 12 –0.8 3.5 12 3.6 0.69 (–0.13, 1.52)
Quaney, 2009 [44] 0.71 4.23 19 –0.28 5.42 19 6.0 0.20 (–0.44, 0.84)
Letombe, 2010 [49] 2.26 1.21 9 0.75 1.5 9 2.4 1.06 (0.05, 2.06)
Ivey, 2010 [51] 2.5 4 29 –0.7 3.6 24 7.7 0.82 (0.26, 1.39)
Moore, 2010 [48] 1 3.2 10 0 5.4 10 3.2 0.22 (–0.66, 1.10)
Ivey, 2011 [52] 2.8 4.9 19 –0.7 3.7 19 5.6 0.79 (0.13, 1.45)
Globas, 2012 [54] 5.5 4.6 18 –0.8 7.8 18 5.1 0.96 (0.27, 1.66)

Total (95% CI) 336 324 100.0 0.55 (0.39, 0.71)

Heterogeneity: \( \chi^2 = 9.09, \text{d.f.} = 14 (p = 0.83), I^2 = 0\% \)
Test for overall effect: \( Z = 6.86 (p < 0.00001) \)

Chu, 2004 [30] 3.9 3 7 0.5 3.2 5 3.8 1.02 (–0.23, 2.27)
Macko, 2005 [32] 2.4 5.1 32 0.2 5.4 29 23.0 0.41 (–0.09, 0.92)
Lee, 2008 [41] 1.5 4.5 12 –0.8 3.5 12 8.9 0.55 (–0.27, 1.37)
Lennon, 2008 [42] 1.4 1.6 23 0 1.8 23 16.3 0.81 (0.20, 1.41)
Quaney, 2009 [44] 0.71 4.23 19 –0.28 5.42 19 14.6 0.20 (–0.44, 0.84)
Moore, 2010 [48] 1 3.2 10 0 5.4 10 7.7 0.22 (–0.66, 1.10)
Ivey, 2011 [52] 2.8 4.9 19 –0.7 3.7 19 13.5 0.79 (0.13, 1.45)
Globas, 2012 [54] 5.5 4.6 18 –0.8 7.8 18 12.3 0.96 (0.27, 1.66)

Total (95% CI) 140 135 100.0 0.58 (0.34, 0.83)

Heterogeneity: \( \chi^2 = 5.01, \text{d.f.} = 7 (p = 0.66), I^2 = 0\% \)
Test for overall effect: \( Z = 4.71 (p < 0.00001) \)
trials (8 studies, SMD = 0.59, p < 0.001; online suppl. fig. 1a), and (3) ischemic stroke aerobic trials (6 studies, SMD = 0.60, p < 0.001; online suppl. fig. 1b).

Eight trials measured peak workload [24, 26, 27, 30, 39, 41, 42, 49]. When all eight trials were analysed, Egger’s regression asymmetry test showed a significant publication bias, and therefore no meta-analysis was done. Next, we included only better-quality aerobic exercise trials and eliminated Bateman et al. [26] because not all subjects in their trial had a diagnosis of stroke. The publication bias no longer existed and the subsequent meta-analysis involving five studies revealed a significant pooled treatment effect on peak workload (SMD = 0.77, p < 0.001; fig. 3).

Five aerobic trials included peak heart rate achieved during the maximal exercise test as an outcome [24, 27, 39, 42, 53]. None of the studies reported a significant effect. The pooled treatment effect, not surprisingly, was not significant (p = 0.50).

Secondary Outcomes
Cardiovascular Health
Body Weight/Body Composition. Body Mass Index [26, 30], body weight [24, 38], fat free mass [38], percent body fat [38] and waist girth [42] were used as outcomes in various studies. No significant treatment effect on these outcomes was reported.

Resting Heart Rate and Blood Pressure. No significant effect was reported on resting heart rate [24, 27, 39, 42, 53] or systolic and diastolic blood pressure at rest [24, 27, 42, 53].

Blood Lipid Profile, Glucose Tolerance and Insulin Sensitivity. Total cholesterol [42] was measured in one study, and no significant effect was found. Ivey et al. [38] found significant reductions in fasting glucose, fasting insulin and the total integrated 3-hour insulin response in the aerobic exercise group relative to the control group.

Leg Blood Flow. Ivey et al. [51] reported that following 6 months of training, both resting and reactive hyperemic blood flow in the calf were significantly increased in both the paretic and non-paretic legs.

Cerebral Blood Flow. Middle cerebral artery blood flow, as measured by transcranial Doppler ultrasonography, was used as an outcome in one study [52]. Significantly better improvement in cerebral vasomotor reactivity in both hemispheres was detected in the aerobic training group compared with controls.

Cardiac Risk Factors. Lennon et al. [42] measured the cardiac risk score, which is an algorithmic score computed based on age, resting blood pressure, smoking status, diabetes status, total cholesterol and high-density lipoprotein scores. Following 10 weeks of aerobic exercise, significantly more reduction in the cardiac risk score was found in the treatment group than the control group.

Functional Performance
Endurance. The primary analysis incorporating all 14 exercise trials that measured walking endurance showed a significant effect in favour of the experimental treatment (SMD = 0.22, p = 0.003; fig. 4a). The significant treatment effect remained in sensitivity analyses involving aerobic trials with PEDro score ≥ 5 only (SMD = 0.31, p = 0.001; fig. 4b). In contrast, mixed aerobic and strength training trials demonstrated no significant effect (SMD = 0.08, p = 0.480; online suppl. fig. 2). Exercise endurance was also evaluated by measuring the total exercise time during the maximal exercise test in four studies [25, 29, 49, 53], three of which reported a significant increase in exercise time in favour of the treatment group [25, 29, 49].

Balance Ability. Aerobic exercise did not induce a significant effect on Berg balance score (BBS; 9 studies, SMD = 0.06, p = 0.52; online suppl. fig. 3a). The result was similar in sensitivity analysis with Bateman et al. [26] excluded (8 studies, SMD = 0.08, p = 0.44; online suppl. fig. 3b). Other studies measured balance using the Timed Up and Go Test [40, 44, 45, 48], Functional Reach Test [29, 40, 50], Postural Assessment Scale for Stroke Patients (PASS) [37] and Four Square Step Test [53]. Significant effect on PASS [37] and TUG [40, 44] was reported by one and two studies, respectively.
Walking Speed. The primary meta-analysis showed that aerobic exercises had a significant effect on maximum walking speed (7 studies, SMD = 0.37, p = 0.005; fig. 5). The results were similar when only aerobic trials with PEDro score ≥5 were analysed (online suppl. fig. 4a). Eight studies measured self-selected walking speed. Because of publication bias, meta-analysis was carried out only for those aerobic trials with PEDro ≥5, and no significant effect was found (online suppl. fig. 4b).

Performance in Daily Activities. No significant effect on Functional Independence Measure (FIM) was found in our meta-analysis (5 studies, SMD = 0.08, p = 0.49; online suppl. fig. 4c). Other studies used Rivermead Motor Score [26, 31, 32, 40, 54], Barthel Index [26, 45, 49], Frenchay Activities Index [28, 42], Nottingham extended Activities of Daily Living [26, 40] and Katz Score [49] to measure functional ability. Significant effect was only found in two studies [49, 54].

Walking Economy. Four studies measured various indexes of energy cost during walking [32, 40, 41, 48]. Only two studies reported significant effect [41, 48].

Physical Activity Level. Two mixed aerobic/strengthening exercise trials included physical activity level as an outcome [25, 34]. No significant results were reported.

Psychological Health

Three studies measured psychological function using the Hospital Anxiety and Depression Scale [26, 40, 42], whereas one measured self-efficacy in walking and stair climbing [41]. None showed significant results.

Cognitive Function

Only Quaney et al. [44] specifically examined the effects of aerobic training on cognitive function. Significant treatment effect was observed in information processing speed on the serial reaction timed task, and predictive force accuracy for a precision grip task.
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental group</th>
<th>Comparison group</th>
<th>Weight %</th>
<th>Std. mean difference IV, fixed (95% CI)</th>
<th>Std. mean difference IV, fixed (95% CI)</th>
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<td>122.8</td>
<td>46</td>
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<td>Pang, 2005 [7]</td>
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<td>Toledano-Zahril, 2011 [53]</td>
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<td>Globas, 2012 [54]</td>
<td>57.7</td>
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<td>368</td>
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<td>0.22 (0.08, 0.37)</td>
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</tr>
</tbody>
</table>

**Heterogeneity:** $\chi^2 = 12.34, \text{d.f.} = 13 (p = 0.50), I^2 = 0$

**Test for overall effect:** $Z = 2.98 (p = 0.003)$

---

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental group</th>
<th>Comparison group</th>
<th>Weight %</th>
<th>Std. mean difference IV, fixed (95% CI)</th>
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<td>223</td>
<td>100.0</td>
<td>0.31 (0.12, 0.50)</td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** $\chi^2 = 2.82, \text{d.f.} = 8 (p = 0.94), I^2 = 0$

**Test for overall effect:** $Z = 3.28 (p = 0.001)$
Quality of Life

Six studies incorporated quality of life measures [25, 36, 40, 41, 45, 54], and only 3 reported significant effects [25, 40, 54].

Relationship between Training Protocol and Outcomes

Comparing the trials that used cycle ergometer versus treadmill as the training modality revealed no significant difference in improvement in peak VO₂ or other outcomes. No significant relationship was identified between the improvement of outcome variables and frequency of training sessions, and duration of each training session (p > 0.05). As the number of trials that used a moderate training intensity with measurement of VO₂ or walking endurance or maximal walking speed is small (≤2 for each outcome) [31, 36, 42], no meaningful comparison could be made between these trials and those that used a high training intensity.

There was also no significant correlation between the effect size of peak VO₂ and that of other functional outcomes (e.g. walking endurance, BBS, FIM), probably due to the relatively small number of studies (≤7 studies) that measured both peak VO₂ and other functional outcomes.

Adverse Effects

Major cardiovascular incidents were rare (online suppl. Appendix 4). Only Duncan et al. [29] and Luft et al. [43] reported a few cases of recurrent stroke (5–6%) in the experimental group.

Discussion

This study provides the most updated review of the current evidence related to the use aerobic exercise in influencing various health indicators in persons living with stroke, and provides foundation for developing evidence-based exercise prescriptions for this client group. The results showed that aerobic exercise of moderate to high intensity conducted for 20–40 min and 3–5 days per week is effective in improving aerobic fitness, maximal walking speed and walking endurance in stroke patients. The effects on other relevant health outcomes require further investigation.

Effect on Aerobic Fitness

Our meta-analyses showed that aerobic training is effective in improving peak VO₂ and peak workload in stroke patients, with medium to large effect sizes. The only study that failed to show a significant effect on aero-
bic fitness was Moore et al. [48]. It is possible that the
4-week training period used in their study may be too
short to induce a substantial cardiovascular effect in
chronic stroke patients, who may have lived an inactive
lifestyle for extended periods. The duration of the exer-
cise programme was at least 8 weeks among other studies
that showed a positive effect on peak VO$_2$ in chronic
stroke patients [24, 32, 33, 38, 42–44, 54]. Despite the in-
crease in peak VO$_2$ and workload as revealed in our meta-
analyses, no significant overall effect on peak heart rate
was found. The results suggest that the improvement in
aerobic fitness may be attributable to the increase in
stroke volume or/and utilization of oxygen by skeletal
muscles, rather than increase in peak heart rate achieved.
Further study is required to investigate the mechanisms
underlying the observed improvement in aerobic ca-
pacity.

**Effect on Functional Performance**

Walking endurance has been identified as a key area
of difficulty among stroke patients [55]. The meta-anal-
ysis also revealed that aerobic exercise is effective in induc-
gain in walking endurance. There is also evidence
that aerobic training is more effective in enhancing walk-
ing endurance than mixed aerobic/strength training. Globas et al. [54] found that improvement in walking en-
durance was significantly related to progression of train-
ing duration. In mixed aerobic/strength training, the ex-
ercise sessions were not entirely devoted to aerobic ac-
tivities, and therefore less time would be available for the
progression of aerobic exercise duration. Nevertheless,
it is encouraging that the improved aerobic fitness can
translate into enhanced performance in such an impor-
tant functional activity.

Another important finding is that aerobic exercise can
improve maximum walking velocity. It should be noted
that a good number of the selected trials involved exercis-
ing on a treadmill. The improvement in walking speed
might be partly attributable to repeated gait practice at a
higher speed. Indeed, Globas et al. [54] found that the de-
gree of improvement in maximum walking speed was sig-
nificantly associated with progression of treadmill ve-
locity and training duration. It is interesting that only
maximum walking speed, but not self-selected walking
speed, was significantly improved after training. Most of
the studies that measured walking speed were chronic
stroke trials in which the subjects had regained indepen-
dent ambulatory function. Indeed, being an independent
ambulator was one of the subject selection criteria for
many of the studies [25, 32, 33–36, 40, 42, 45, 48, 50–52,
54]. Further improvement in walking speed after exercise
training may be more apparent when the participants are
asked to perform a more demanding walking task.

The meta-analyses showed that aerobic exercise has no
significant effect on BBS and FIM scores. It is well known
that BBS has a substantial ceiling effect among stroke pa-
tients who have regained ambulatory function [56]. It is
thus difficult to detect further improvement in balance
ability among these patients following exercise training.
On the other hand, FIM score measures the indepen-
dence level in performing a wide range of daily activities,
some of which are less likely to be influenced by exercise
training (e.g. eating, grooming, swallowing, bowel and
bladder management). Katz-Leurer et al. [37] reported
both FIM total and motor scores, and found that signifi-
cant treatment effect was only detected in FIM motor
score. These results point to the importance of selecting
appropriate and responsive outcome measures that can
capture the changes in functional performance in these
patients in future aerobic exercise trials.

**Effect on Other Outcomes**

The effect of aerobic training on other outcomes in
cardiovascular health, psychological and cognitive func-
tioning is inconclusive, because only a small number of
studies incorporated these outcomes. Six studies mea-
ured quality of life, but only three reported significant
findings [25, 40, 54]. It is, however, difficult to compare
the results across the different studies because of the dif-
ferent instruments used to measure quality of life. Over-
all, more research is required to investigate the effects of
aerobic exercise on these important outcomes.

**Relationship between Training Parameters and
Treatment Effect**

Our review did not reveal any relationship between
the magnitude of the treatment effect obtained and vari-
ous aspects of the training protocols (duration, frequen-
cy, modality, etc.), probably due to the fact that the treat-
ment protocols used in various studies differed in a num-
ber of aspects, which made it difficult to delineate the
influence of a particular variable on a given outcome.
However, Globas et al. [54] showed that the gain in peak
VO$_2$ was significantly correlated with the degree at which
training intensity could be progressed. In a non-random-
ized controlled trial not included in this review, Rimmer
et al. [57] found that exercise at moderate intensity (up to
60–69% HRR) for a shorter duration (30 min) induced
more favourable effects on resting systolic and diastolic
blood pressure and total cholesterol compared with exer-
exercise at lower intensity (below 50% HRR) for a longer duration (up to 60 min) and conventional exercise, thus highlighting the importance of training intensity. Taken together, exercise intensity seems to be an important predictor of the response to aerobic exercise intervention.

In addition to training intensity, other training parameters (e.g. duration and frequency of exercise sessions) may also influence the therapeutic effects and the influence may be specific to the outcomes measured. As aforementioned, while improvement in peak VO₂ was related to progression of exercise intensity, Globas et al. [54] found that improvement in walking endurance was more related to progression of treadmill speed and duration than training intensity. Subject characteristics may also have a major impact on the response to aerobic exercise. Indeed, in a post hoc analysis involving two RCTs [43, 54], Lam et al. [58] showed that improvement in walking endurance was greater among those with more recent strokes and left-sided lesions. It is likely that the response to aerobic exercise training is highly individualized, depending upon not only the treatment protocol, but also subject characteristics and the outcome measure used.

**Safety Issues**

The reported adverse events were few. Isolated cases of recurrent stroke (5–6%) were reported by Duncan et al. [29] and Luft et al. [43]. It is unlikely that the exercise training itself contributed to the recurrent strokes because the incidence rate of recurrent stroke reported was comparable to that in the general stroke population (annual risk = 4–10%) [2, 59]. However, exercising the stroke patients at moderate to high intensities may still raise some safety concerns. It may be particularly relevant to patients with haemorrhagic stroke, who often have problems with blood pressure control. In most trials (72%), it was explicitly stated that subjects underwent a maximal exercise testing session to screen out any significant cardiovascular signs and symptoms before participating in exercise training (online suppl. Appendix 3). In all trials, strict eligibility criteria were in place, excluding those individuals with substantial cardiovascular risk factors (online suppl. Appendix 3).

**Practical Suggestions for Aerobic Exercise Programming**

The findings of this review can have important contributions to establishing clinical guidelines for aerobic exercise prescription among stroke patients. Firstly, to identify suitable candidates for aerobic exercise training, some form of cardiovascular screening should be incorporated. The patients should undergo thorough screening to identify not only general health problems that may limit the ability to engage in aerobic training, but also the cardiovascular risk factors that may pose safety concerns. Ideally, cardiac screening using a maximal exercise test with electrocardiographic and blood pressure monitoring should be carried out [60]. The American College of Sports Medicine (ACSM) criteria can be used to determine the suitability of the patients to participate in training [12].

The most commonly used duration and frequency of exercise sessions was 20–30 min and 3–5 sessions per week, respectively. However, for those with poor exercise tolerance at the beginning, short exercise bouts (e.g. 2 min) may be given, with interspersed rest periods [27, 39]. As exercise tolerance improves, longer periods of continuous exercise with shorter rest periods should be implemented. The goal is to increase the duration of continuous exercise up to 20–40 min.

Over 60% of the studies used a high target training intensity (60–80% HRR), although a good number of trials did use a moderate intensity initially (40–50% HRR) and progressively increased the exercise intensity [32, 34, 38, 41, 43, 44, 50–52, 54], often at 5% every 2 weeks as tolerated over the course of the training programme. The initial training intensity and subsequent progression should be individualized, depending upon the individual’s ability, subjective responses to treatment (e.g. rate of perceived exertion, etc.) and objective findings (heart rate and blood pressure responses, etc.) [60]. Although a training intensity at 40% HRR is not adequate to induce a positive training effect among chronic stroke patients with independent ambulatory function [32], it cannot be ruled out that a lower training intensity may benefit those with more severe physical impairments [61]. According to ACSM guidelines, exercising at 30% HRR may be used initially for those who are severely deconditioned [12]. It is also important to emphasize that the determination of target exercise intensity should be based on the maximal heart rate achieved in the maximal exercise test, as specifically stated in the majority of studies. It would not be appropriate to use age-predicted maximal heart rate, because it is known that the heart rate achieved in the maximal exercise test for most stroke patients is well below the age-predicted maximal heart rate [62]. Using the age-predicted maximal heart rate to determine the exercise intensity would likely result in having the patient exercise at a much higher intensity than intended.

Treadmill and cycle ergometer are popular modalities used for aerobic training. The choice of modality highly
depends upon individual ability and preference, as well as safety. For example, among those with poorer standing balance, cycle ergometer may be a good option as it requires less postural control. Treadmill training with body weight support can also be provided to facilitate an upright posture. Functional movements that involve large muscle groups may also be used for aerobic training, such as sit-to-stand and brisk over-ground walking [33].

Both hospital/clinic-based [24–28, 30–32, 37–40, 42–44, 45–54] and community/home-based settings were used for exercise training [29, 34, 45–47]. For higher-risk individuals or those with acute stroke, the training should be supervised by qualified individuals in a clinical setting. In lower-risk individuals (e.g. chronic stroke patients who are medically stable), the supervised training can take place in the community or the individual’s own home [60].

Finally, to assess treatment effects of the program, peak VO$_2$ is considered as a gold standard for measuring cardiovascular fitness, but its measurement requires sophisticated equipment that may not be readily available in many clinical settings. Six Minute Walk Test is an alternative outcome measure to indicate aerobic capacity, as it has been shown that in stroke patients, particularly those with better ambulatory function, the distance covered in the test is moderately correlated with peak VO$_2$ [8]. The outcome assessment should cover not only body functions, but also activity and participation. Other outcomes related to daily functioning, such as the maximal walking speed, FIM motor score and quality of life (e.g. Nottingham Health Profile), may also be used. Table 3 summarizes the practical suggestions on aerobic exercise programming based on the evidence obtained in this review.

**Limitations of the Studies Reviewed**

While over half of the studies included in this systematic review were considered good quality studies (PEDro score >5), none of the studies fulfilled the criteria of ‘subject blinding’ and ‘therapist blinding’. These factors may reduce the internal validity. Understandably, it is very difficult to meet these criteria in exercise trials compared with drug trials. External validity (or generalizability) is another issue. The results of each individual study can

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**Table 3. Practical suggestions for clinical programming**

<table>
<thead>
<tr>
<th>Practical suggestions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient screening</strong></td>
</tr>
<tr>
<td>- The medical record should be reviewed to identify health problems that may limit the ability to engage in aerobic training</td>
</tr>
<tr>
<td>- ACSM criteria can be used for cardiac screening</td>
</tr>
<tr>
<td>- Cardiac screening using a maximal exercise test with electrocardiographic and blood pressure monitoring is required</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
</tr>
<tr>
<td>- Higher-risk individuals or those with acute stroke: supervised training in clinical setting</td>
</tr>
<tr>
<td>- Lower-risk individuals (e.g. chronic stroke patients who are medically stable): supervised training in community or individual’s own home</td>
</tr>
<tr>
<td><strong>Training modality</strong></td>
</tr>
<tr>
<td>- Treadmill, cycle ergometer, or functional activities (e.g., brisk over-ground walking, sit-to-stand)</td>
</tr>
<tr>
<td>- Body weight support may be provided during treadmill training</td>
</tr>
<tr>
<td><strong>Intensity</strong></td>
</tr>
<tr>
<td>- Initially: 40–50% HRR (or lower for extremely deconditioned individuals)</td>
</tr>
<tr>
<td>- Final target: 60–80% HRR</td>
</tr>
<tr>
<td>- A heart rate monitor should be worn</td>
</tr>
<tr>
<td>- Sporadic blood pressure monitoring is recommended</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
</tr>
<tr>
<td>- 3–5 days per week</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
</tr>
<tr>
<td>- 20–40 min of continuous exercise per session</td>
</tr>
<tr>
<td>- Initially, may use short exercise bouts (e.g. 2 min), with interspersed rest periods [27, 39]</td>
</tr>
<tr>
<td>- Longer periods of continuous exercise with shorter rest periods should be used as exercise endurance improves</td>
</tr>
<tr>
<td><strong>Assessment of treatment effect</strong></td>
</tr>
<tr>
<td>- Peak VO$_2$</td>
</tr>
<tr>
<td>- Six Minute Walk Test</td>
</tr>
<tr>
<td>- Maximal walking speed</td>
</tr>
<tr>
<td>- Activity and participation: e.g. FIM motor score</td>
</tr>
<tr>
<td>- Quality of life measures: e.g. Nottingham Health Profile</td>
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</table>
only be generalized to those who have characteristics similar to the study sample itself. It is thus critical that the subject selection criteria are clearly described. It was found that two selected studies did not clearly specify the eligibility criteria [24, 45] (table 1). External validity, however, was not included in the calculation of the PEDro score. A high PEDro score thus did not necessarily indicate high external validity. Finally, a few studies had small sample sizes (20 subjects or less), which led to concerns regarding reduced statistical power and representativeness of the sample [30, 48, 49].

Limitations of the Systematic Review
Firstly, no recommendation can be given for the use of aerobic exercise on improving many outcomes of interest (i.e. activities of daily living, psychosocial function, cognitive function, quality of life, etc.), due to the limited number of relevant studies. Secondly, all of the selected studies are RCTs, because it is the best study design to establish cause and effect. The majority of the selected studies had strict inclusion and exclusion subject selection criteria (online suppl. Appendix 3). While the increase in experimental control may improve the internal validity, it may limit the external validity. The results of the systematic review can only be generalized to a subpopulation of stroke patients who are mildly or moderately impaired by stroke, with relatively low risk of cardiovascular complications with exercise.

Conclusion
Based on the available research evidence, the effect of aerobic exercise on aerobic fitness, maximal walking speed and walking endurance in stroke patients is supported by consistent level 1 and 2 evidence. The health risk associated with engaging in such exercise is small. Persons living with a mild to moderate stroke who were deemed to have low cardiovascular risk with exercise after proper screening assessments should be encouraged to engage in aerobic exercise on a routine basis (40–50% HRR progressing to 60–80% HRR, 3–5 days a week for 20–40 min) to improve the above outcomes (grade A recommendation).

Acknowledgements
This article was part of a large evidence-based consensus process to develop evidence-based physical activity prescriptions for prominent health conditions. The lead investigators on this project are Dr. Darren Warburton, Dr. Norman Gledhill, Dr. Roni Jamnik, Dr. Don McKenzie and Dr. Shannon S.D. Bredin. The primary funding for this article and this project was provided to the lead investigators through a financial contribution from the Public Health Agency of Canada. Further funding for this project was made available to Dr. Shannon Bredin and the Physical Activity Line (www.physicalactivityline.com) from the Public Health Agency of Canada British Columbia division. All articles were required to adhere to the standards established by the ‘Appraisal of Guidelines for Research and Evaluation’ (AGREE) assessment tool/process. As part of the AGREE process, all articles undergo an external review from at least two international authorities and a further review by the consensus panel (consisting of Dr. Warburton, Dr. Gledhill, Dr. Jamnik, Dr. McKenzie, Dr. James Stone and Dr. Roy Shephard) as described elsewhere [16, 17]. In addition to adhering to the AGREE process, the physical activity prescriptions were assigned a standardized Level of Evidence (1 = RCTs; 2 = RCTs with limitations or observational trials with overwhelming evidence; 3 = observational studies; 4 = anecdotal evidence) and a standardized Grade of Evidence (A = strong; B = intermediate; C = weak) as detailed elsewhere [16, 17]. This article provides the foundation for developing evidence-based physical activity prescriptions for persons living with stroke.

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Disclosure Statement
The authors declare no conflict of interest.

References
Cardiovascular Exercise in Stroke


