Article Title:

Using aerobic exercise to improve health outcomes and quality of life in stroke: Evidence-based exercise prescription recommendations

Running head:

Cardiovascular exercise in stroke

Authors and affiliations:

Marco Y.C. Pang (PhD), Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Kowloon, Hong Kong

Sarah A. Charlesworth (PhD), Cardiovascular Physiology and Rehabilitation Laboratory, University of British Columbia, Physical Activity Promotion and Chronic Disease Prevention Unit, Vancouver, BC, Canada.

Ricky W. K. Lau (PhD), Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Kowloon, Hong Kong.

Raymond C. K. Chung (PhD), Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong.

FULL ADDRESS

Corresponding Author:

Dr. Marco YC Pang, Associate Professor, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong.

Fax: 852-2330-8656, Telephone: 852-2766-7156, Email: Marco.Pang@inet.polyu.edu.hk

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 and 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.

Results: Twenty five trials fulfilled the selection criteria, of which 8 are 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 minutes 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 ($p<0.001$), peak workload ($p<0.001$), maximal gait speed ($p=0.003$), and walking endurance

($p<0.001$) in favour of aerobic exercise. Meta-analysis revealed no significant effect on self-selected gait speed, Berg balance score, and Functional Independence Measure (FIM) score. The efficacy of aerobic exercise in improving other health outcomes in physical, psychosocial, and cognitive domains, and 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% heart rate reserve progressing to 60-80%) conducted 20-40 minutes, and 3-5 days per week is beneficial for enhancing aerobic fitness, walking speed, and walking endurance in people who have 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.

INTRODUCTION

Stroke is one of the most common disabling conditions worldwide. The various physical impairments that ensue from the 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 value 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 foregoing study question. The inclusion criteria were: randomized controlled trials (RCT) that investigated the effects of aerobic exercise in stroke patients; the aerobic training protocol was clearly described (e.g., intensity); studies 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 was 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 stages of stroke were defined as 0-1, 1-6, and more than 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 (BMI), body composition, waist girth, resting heart rate (HR) and blood pressure (BP), 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 PsychoINFO. The specific search strategy for the MEDLINE database is described in Supplementary Appendix 1. 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 on October, 2011. For these databases, the keyword "stroke" was entered to search relevant articles. 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 excellent by PEDro and sample size >50) are considered level 1 evidence whereas lower-quality RCTs are 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). 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 of less than 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 deviations (SDs) for each of the 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 11539 articles were generated from the aforementioned search strategy after removing the duplicates (Figure 1). Sixty-seven articles were eliminated after reading the full text (Supplementary 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. [33-36] 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 studied only 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 (Supplementary Appendix 3). Individuals with significant cardiovascular conditions (e.g., uncontrolled hypertension, peripheral vascular diseases, etc.) were not enrolled (Supplementary 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 minutes 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 (HRmax)] [24,27,30,32,33,38,39,40,42-44,48,50-52,54]. The details of the treatment protocols and outcomes are provided in Supplementary Appendix 4.

Primary outcomes

Aerobic fitness

In our primary meta-analysis incorporating all 15 trials that measured peak VO_2, a significant beneficial effect of the aerobic exercise was found (SMD=0.55, $p<0.001$)(Figure 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, $p<0.001$) (Figure 2B), (2) chronic stroke aerobic trials (8 studies, SMD=0.59, $p<0.001$) (Supplementary Figure

1A), and (3) ischemic stroke aerobic trials (6 studies, SMD=0.60, p<0.001) (Supplementary Figure 1B).

Eight trials measured peak workload [24,26,27,30,39,41,42,49]. When all eight trials were analyzed, 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) (Figure 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: BMI [26,30], body weight [24,38], fat fee 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], systolic and diastolic BP 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 six 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 BP, smoking status, diabetes status, total cholesterol, and high-density lipoprotein scores. Following 10 weeks of aerobic exercise, significant 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) (Figure 4A). The significant treatment effect remained in sensitivity analyses involving aerobic trials with PEDro score ≥5 only (SMD=0.31, p=0.001) (Figure 4B). In contrast, mixed aerobic and strength training trials demonstrated no significant effect (SMD=0.08, p=0.480)(Supplementary figure 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) (Supplementary figure 3A). The result was similar in sensitivity analysis with Batemen et al. excluded [26] (8 studies, SMD=0.08, p=0.44) (Supplementary figure 3B). Other studies measured balance using 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 significant effect on maximum walking speed (7 studies, SMD=0.37, p=0.005)(Figure 5). The results were similar when only aerobic trials with PEDro score ≥5 were analyzed (Supplementary figure 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 (Supplementary figure 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)(Supplementary figure 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 psychologic function using the Hospital Anxiety and Depression Scale (HADS) [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.

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 Vs treadmill as the training modality revealed no significant difference in improvement in peak VO_2 and 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 VO_2 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 VO_2 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 VO_2 and other functional outcomes.

Adverse effects

Major cardiovascular incidents were rare (Supplementary 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 20-40 minutes, and 3-5 days per week is effective in improving aerobic fitness, maximal walking speed, and walking endurance in stroke pateints. 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 VO_2 and peak workload in stroke patients, with medium to large effect sizes. The only study that failed to show a significant effect on aerobic 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 exercise 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 increase 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 hear rate achieved. Further study is required to investigate the mechanisms underlying the observed improvement in aerobic capacity.

Effect on functional performance

Walking endurance has been identified as a key area of difficulty among stroke patients [55].The meta-analysis also revealed that aerobic exercise is effective in inducing gain in walking endurance. There is also evidence that aerobic training is more effective in enhancing walking endurance than mixed aerobic/strength training. Globas et al. [54] found that improvement in walking endurance was significantly related to progression of training duration. In mixed aerobic/strength training, the exercise sessions were not entirely devoted to aerobic activities, 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 important 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 exercising 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 degree of improvement in maximum walking speed was significantly associated with progression of treadmill velocity 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 are chronic stroke trials, and the subjects had regained independent 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 substantial ceiling effect among stroke patients 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 independence 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 significant 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, psychologic and cognitive functioning is inconclusive, because only a small number of studies incorporated these outcomes. Six studies measured 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 different instruments used to measure quality of life. Overall, 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 various aspects of the training protocols (duration, frequency, modality, etc.), probably due to the fact that the treatment protocols used in various studies differed in a number 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-randomized controlled trial not included in this review, Rimmer et al. [57] found that exercise at moderate intensity (up to 60-69% HRR) for shorter duration (30 minutes) induced more favourable effects on resting systolic and diastolic blood pressure, and total cholesterol compared with exercise at lower intensity (below 50%HRR) for longer duration (up to 60 minutes) 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 VO_2 is 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 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 contributes 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 hemorrhagic stroke patients, 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 (Supplementary Appendix 3). In all trials, strict eligibility criteria were in place, excluding those individuals with substantial cardiovascular risk factors (Supplementary 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 minutes and 3-5 sessions per week, respectively. However, for those with poor exercise tolerance at the beginning, short exercise bouts (e.g., 2 minutes) 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 minutes.

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 increase 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 (HR and blood pressure responses, etc.). 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 erogmeter 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 overground 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.

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 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, is not

included in the calculation of the PEDro score. A high PEDro score does not necessarily indicate high external validity. Finally, a few studies have 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 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. Majority of the selected studies had strict inclusion and exclusion subject selection criteria (Supplementary 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 sub-population of stroke patients who are mildly or moderately impaired by stroke, with relatively low risk of cardiac 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 minutes) 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.

SOURCES OF FUNDING

The primary funding for this article was provided to MYC Pang and S Charlesworth through a financial contribution from the Public Health Agency of Canada.

DISCLOSURES/CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Michael KM, Allen JK, Macko RF: Reduced ambulatory activity after stroke: the role of balance, gait, and cardiovascular fitness. Arch Phys Med Rehabil 2005;86:1552-1556.
2. Weimar C, Bennemann J, Michalski D, Muller M, Luckner K, Katsarava Z, Weber R, Diener H-C: Prediction of recurrent stroke and vascular health in patients with transient ischemic attack or nondisabling stroke: a prospective comparison of validated prognostic scores. Stroke 2010;41:487-493.
3. Appelros P, Gunnarsson KE, Terent A: Ten-year risk for myocardial infarction in patients with first-ever stroke: a community-based study. Acta Neurol Scand 2011;124:383-389.
4. Kuwashiro T, Sugimori H, Ago T, Kamouchi M, Kitazono T: Risk Factors Predisposing to Stroke Recurrence within One Year of Non-Cardioembolic Stroke Onset: The Fukuoka Stroke Registry. Cerebrovasc Dis 2012;33:141-149.
5. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C: Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke 2004;35:731-735.
6. MacKay-Lyons MJ, Makrides L. Longitudinal changes in exercise capacity after stroke. Arch Phys Med Rehabil. 2004;85:1608-1612.
7. Pang MYC, Eng JJ, Dawson AS: Relationship between ambulatory capacity and cardiorespiratory fitness in chronic stroke: influence of stroke-specific impairments. Chest 2005;127:495-501.
8. Patterson SL, Forrester LW, Rodgers MM, Ryan AS, Ivey FM, Sorkin JD, Macko RF: Determinants of walking function after stroke: differences by deficit severity. Arch Phys Med Rehabil 2007;88:115-119.

9. Kelly JO, Kilbreath SL, Davis GM, Zeman B, Raymond J: Cardiorespiratory fitness and walking ability in subacute stroke patients. Arch Phys Med Rehabil 2003;84:1780-1785.
10. Cress ME, Meyer M: Maximal voluntary and functional performance levels needed for independence in adults aged 65 to 97 years. Phys Ther 2003;83:37-48.
11. Cebm.net [Internet]. Oxford: Oxford Centre for Evidence-based Medicine; c2012 [updated 2012 March 29; cited 2012 Apr 8]. Available from: http://www.cebm.net/.
12. American College of Sports Medicine: ACSM's guidelines for exercise testing and prescription. 8th ed. Baltimore, Wolters Kluwer/Lippincott Williams & Wilkins, 2010.
13. Paillard T: Combined application of neuromuscular electrical stimulation and voluntary muscular contractions. Sports Med 2008;38:161-177.
14. pedro.org.au [Internet]. Sydney: The Centre of Evidence-Based Physiotherapy; c2012 [updated 2012 Apr 2; cited 2012 Apr 8]. Available from: http://www.pedro.org.au/.
15. Bhogal SK, Teasell RW, Foley NC, Speechley MR: The PEDro scale provides a more comprehensive measure of methodological quality than the Jadad scale in stroke rehabilitation literature. J Clin Epidemiol 2005;58:668-673.
16. Warburton DER, Gledhill N, Jamnik VK, Bredin, SSD, McKenzie DC, Stone J, Charlesworth S, Shephard RJ: Evidence-based risk assessment and recommendations for physical activity clearance: Consensus Document 2011. Appl Physiol Nutr Metab 2011;36:S266-298.
17. Jamnik VJ, Warburton DER, Makarski J, McKenzie DC, Shephard RJ, Stone J, Charlesworth S, Gledhill N: Enhancing the effectiveness of clearance for physical activity participation; background and overall process. Appl Physiol Nutr Metab 2011;36:S3-13.

18. Mayer D: Essential evidence-based medicine. Cambridge, University Press, 2004.

19. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634.

20. Hedges L: Fixed effects models. in Cooper H, Hedges LV (eds): The Handbook of Research Synthesis. New York, Russell Sage Foundation, 1994, pp 285-300.

21. Harris JE, Eng JJ: Strength training improves upper-limb function in individuals with stroke: a meta-analysis. Stroke 2010;41:136-40.

22. Kwakkel G, van Peppen R, Wagenaar RC, Wood Dauphinee S, Richards C, Ashburn A, Miller K, Lincoln N, Partridge C, Wellwood I, Langhorne P: Effects of augmented exercise therapy time after stroke. A meta-analysis. Stroke 2004;35:2529-2536.

23. Cohen J: The t test for means. in Cohen J (ed): Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Hillsdale, Lawrence Erlbaum Associates, Inc., 1988, pp 25-26.

24. Potempa K, Lopez M, Braun LT, Szidon JP, Fogg L, Tincknell T: Physiological outcomes of aerobic exercise training in hemiparetic stroke patients. Stroke 1995;26:101-105.

25. Teixeira-Salmela LF, Olney SJ, Nadeau S, Brouwer B: Muscle strengthening and physical conditioning to reduce impairment and disability in chronic stroke survivors. Arch Phys Med Rehabil 1999;80:1211-1218.

26. Bateman A, Culpan FJ, Pickering AD, Powell JH, Scott OM, Greenwood RJ: The effect of aerobic training on rehabilitation outcomes after recent severe brain injury: a randomized controlled evaluation. Arch Phys Med Rehabil 2001;82:174-182.

27. Katz-Leurer M, Shochina M, Carmeli E, Friedlander Y: The influence of early aerobic training on the functional capacity in patients with cerebrovascular accident at the subacute stage. Arch Phys Med Rehabil 2003;84:1609-1614.

28. Katz-Leurer M, Carmeli E, Shochina M: The effect of early aerobic training on independence six months post stroke. Clin Rehabil 2003;17:735-741.

29. Duncan P, Studenski S, Richards L, Gollub S, Lai SM, Reker D, Perera S, Yates J, Koch V, Rigler S, Johnson D: Randomized clinical trial of therapeutic exercise in subacute stroke. Stroke 2003;34:2173-2180.

30. Chu KS, Eng JJ, Dawson AS, Harris JE, Ozkaplan A, Gylfadottir S: Water-based exercise for cardiovascular fitness in people with chronic stroke: a randomized controlled trial. Arch Phys Med Rehabil 2004;85:870-874.

31. Eich HJ, Mach H, Werner C, Hesse S: Aerobic treadmill plus Bobath walking training improves walking in subacute stroke: a randomized controlled trial. Clin Rehabil 2004;18:640-651.

32. Macko RF, Ivey FM, Forrester LW, Hanley D, Sorkin JD, Katzel LI, Silver KH, Goldberg AP: Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. Stroke 2005; 36: 2206-11.

33. Pang MYC, Ashe MA, Eng JJ, McKay HA, Dawson AS: A 19-week exercise program for people with chronic stroke enhances bone geometry at the tibia: a pQCT study. Osteoporos Int 2006;17:1615-1625.

34. Pang MY, Eng JJ, Dawson AS, McKay HA, Harris JE: A community-based fitness and mobility exercise program for older adults with chronic stroke: a randomized, controlled trial. J Am Geriatr Soc 2005;53:1667-1674.

35. Pang MYC, Eng JJ: Determinants of Improvement in walking capacity among individuals with chronic stroke following a multidimensional exercise program. J Rehabil Med 2008;40:284-290.

36. Eng JJ, Pang MYC, Ashe MA: Balance, falls, and bone health: Role of exercise in reducing fracture risk after stroke. J Rehabil Res Dev 2008;45:297-314.

37. Katz-Leurer M, Sender I, Ofer K, Zeevi D: The influence of early cycling training on balance in stroke patients at the subacute stage. Clin Rehabil 2006;20:398-405.

38. Ivey FM, Ryan AS, Hafer-Macko CE, Goldberg AP, Macko RF: Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: a preliminary report. Stroke 2007;38:2752-2758.

39. Katz-Leurer M, Shochina M: The influence of autonomic impairment on aerobic exercise outcome in stroke patients. Neurorehabilitation 2007;22:267-272.

40. Mead GE, Greig CA, Cunningham I, Lewis SJ, Dinan S, Saunders DH, Fitzsimons C, Young A: Stroke: a randomized trial of exercise or relaxation. J Am Geriatr Soc 2008;5:892-899.

41. Lee MJ, Kilbreath SL, Singh MF, Zeman B, Lord SR, Raymond J, Davis GM: Comparison of effect of aerobic cycle training and progressive resistance training on walking ability after stroke: a randomized sham exercise-controlled study. J Am Geriatr Soc 2008;56:976-985.

42. Lennon O, Carey A, Gaffney N, Stephenson J, Blake C: A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population. Clin Rehabil 2008;22:125-133.
43. Luft AR, Macko RF, Forrester LW, Villagra F, Ivey F, Sorkin JD, Whitall J, McCombe-Waller S, Katzel L, Goldberg AP, Hanley DF: Treadmill exercise activates subcortical neural networks and improves walking after stroke. A randomized controlled trial. Stroke 2008:39:3341-3350.
44. Quaney BM, Boyd LA, McDowd JM, Zahner LH, He J, Mayo MS, Macko RF: Aerobic exercise improves cognition and motor function poststroke. Neurorehabil Neural Repair 2009;23:879-885.
45. Langhammer B, Stanghelle JK, Lindmark B: An evaluation of two different exercise regimes during the first year following stroke: a randomised controlled trial. Physiother Theor Pract 2009;25:55-68.
46. Langhammer B, Lindmark B, Stanghelle JK: Stroke patients and long-term training: is it worthwhile: a randomized comparison of two different training strategies after rehabilitation. Clin Rehabil 2007;21:495-510.
47. Langhammer B, Stanghelle JK, Lindmark B: Exercise and health-related quality of life during the first year following acute stroke: a randomized controlled trial. Brain Inj 2008;22:135-145.
48. Moore JL, Roth EJ, Killian C, Hornby TG: Locomotor training improves daily stepping activity and gait efficiency in individuals poststroke who have reached a "plateau" in recovery. Stroke 2010;41:129-135.

49. Letombe A, Cornille C, Delahaye H, Khaled A, Morice O, Tomaszewski A, Olivier N: Early post-stroke physical conditioning in hemiplegic patients: A preliminary study. Ann Phys Rehabil Med 2010;53:632-642.

50. Outermans JC, van Peppen R, Wittink H, Takken T, Kwakkel G: Effects of a high-intensity task-oriented training on gait performance early after stroke: a pilot study. Clin Rehabil 2010;24:979-987.

51. Ivey FM, Hafer-Macko CE, Ryan AS, Macko RF: Impaired leg vasodilatory function after stroke. Adaptations with treadmill exercise training. Stroke 2010;41:2913-2917.

52. Ivey FM, Ryan AS, Hafer-Macko CE, Macko RF: Improved cerebral vasomotor reactivity after exercise training in hemiparetic stroke survivors. Stroke 2011;42:1994-2000.

53. Toledano-Zarhi A, Tanne D, Carmeli E, Katz-Leurer M: Feasibility, safety and efficacy of an early aerobic rehabilitation program for patients after minor ischemic stroke: A pilot randomized controlled trial. NeuroRehabilitation 2011;28:85-90.

54. Globas C, Becker C, Cerny J, Lam JM, Lindemann U, Forrester LW, Macko RF, Luft AR: Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized controlled trial. Neurorehabil Neural Repair 2012;26:85-95.

55. Mayo NE, Wood-Dauphinee S, Ahmed S, Gordon C, Higgins J, McEwen S, Salbach N: Disablement following stroke. Disability Rehabil 1999;21:258-268.

56. Mao HF, Hsueh IP, Tang PF, Sheu CF, Hsieh CL: Analysis and comparison of the psychometric properties of three balance measures for stroke patients. Stroke 2002;33:1022-1027.

57. Rimmer JH, Rauworth AE, Wang EC, Nicola TL, Hill B: A Preliminary Study to Examine the Effects of Aerobic and Therapeutic (Nonaerobic) Exercise on Cardiorespiratory Fitness and Coronary Risk Reduction in Stroke Survivors. Arch Phys Med Rehabil 2009;90:407-412.

58. Lam JM, Globas C, Cerny J, Hertler B, Uludag K, Forrester LW, Macko RF, Hanley DF, Becker C, Luft AR: Predictors of response to treadmill exercise in stroke survivors. Neurorehabil Neural Repair 2010;24:567-574.

59. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C: Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke 2004;35:731-735.

60. Mackay-Lyons MJ, Macko R, Howlett J: Cardiovascular fitness and adaptations to aerobic training after stroke. Physiother Can 2006;58:103-113.

61. Swain DP, Franklin BA: VO_2 reserve and the minimal intensity for improving cardiorespiratory fitness. Med Sci Sports Exerc 2002;34:152-157.

62. Tang A, Sibley KM, Thomas SG, McIlroy WE, Brooks D: Maximal exercise test results in subacute stroke. Arch Phys Med Rehabil 2006;87:1100-1105.

FIGURE LEGENDS

Figure 1. Flow diagram of article selection process.

A total of 31 articles (25 randomized controlled trials) fulfilled the selection criteria.

Figure 2. Meta-analysis: peak oxygen consumption (primary analysis and sensitivity analysis)

A: Primary analysis incorporating both aerobic and combined aerobic/strengthening trials. For Lee et al. [41], the data of the experimental treatment were based on the pooled effect of the aerobic group and combined aerobic/strengthening group whereas those of the comparison group were derived from the no-intervention control group. B: Analysis involving those aerobic exercise trials with a PEDro score ≥5. The data of the aerobic group in Lee et al. [41] were used for this analysis. Both meta-analysis models showed significant effects on peak VO_2 in favour of the experimental treatment. Each set of dot (■) and error bars represent the standardized mean difference (SMD) value and its 95% confidence interval (CI), respectively, for each study. The first author, the sample size, the change score (post-test score minus pre-test score), and standard deviation of the pre-test score for each of the experimental and comparison groups, the SMD value and its 95% CI of each study were also indicated beside each respective set of dot and error bars. The pooled SMD was indicated by ♦. This convention was used in all other forest plots.

Figure 3. Meta-analysis: peak workload

Significant treatment effect on peak workload was found in the aerobic trials with a PEDro score ≥5.

Figure 4. Meta-analysis: walking endurance (primary analysis and sensitivity analysis)

A: Primary analysis including both aerobic and combined aerobic/strengthening trials. For Lee et al. [41], the data of the experimental treatment were based on the pooled effect of the aerobic group and combined aerobic/strengthening group whereas those of the comparison group were derived from the no-intervention control group. B: Aerobic exercise trials with PEDro score ≥5 only, the data of the aerobic group in Lee et al. [41] were used for this analysis.

Figure 5. Meta-analysis: maximal walking speed

Primary analysis including all trials that measured maximal walking speed is shown. Significant effect was found. The data of the combined aerobic/strengthening group in Lee et al. [41] were used for these analyses.

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

	Number of studies	% of studies	References
METHODOLOGICAL QUALITY			
PEDro rating criteria			
1. Eligibility criteria specified*	23	92	25-44,48-54
2. Random allocation to groups	25	100	24-54
3. Concealed allocation	11	44	26,29,31,33,40-42,45,48,50,54
4. Groups similar at baseline	24	96	24,26-54
5. Subject blinding	0	0	
6. Therapist blinding	0	0	
7. Assessor blinding	12	48	26-33,37,41-45
8. Less than 15% dropouts	16	64	27-31,33,37,39-42,44,45,49,52-54
9. Intent-to-treat analysis	13	52	26,29,31,33,38,40-42,45,49,50,53-54
10. Between groups statistics reported	25	100	24-54
11. Point estimates and variability data reported	25	100	24-54
PEDro total score			
Excellent (9-10)	0	0	
Good (6-8)	16	64	26-31,33,37,40-42,44,45,49,50,53,54
Fair (4-5)	8	32	24,32,38,39,43,48,51,52
Poor (0-3)	1	4	25
Sample size (n)			
≤50 subjects	12	48	24,25,30,31,37,44,48-50,52-54
>50 subjects	13	52	26-29,32,33-36,38-43,45,51
Level of evidence (no. of studies)			
Level 1	8	32	26-29,33,40-42,45
Level 2	17	68	24,25,30-32,37-39,43,44,48-54
STROKE CHARACTERISTICS			
Stage of stroke recovery			
Acute	4	16	27,39,49,53
Subacute	2	8	29,37
Chronic	13	52	24,25,30,32,33,38,42-44,48,51,52,54
Acute + subacute	3	12	31,45,50
Subacute + chronic	2	8	40,41
Acute + subacute + chronic	1	4	26
Stroke type			
Ischemic only	12	48	31,32,37-39,42-44,51-54
Hemorrhagic only	0	0	
Ischemic + hemorrhagic	9	36	27,29,30,33,40,41,45,48,49
Not reported	4	16	24-26,50

*This item is rated as Yes or No, and is not used for calculation of the total PEDro score.

Table 2. Summary: aerobic exercise protocols

	Number of studies	% of studies	References
Modality used for aerobic exercise			
Cycle ergometer	10	40	24,26,27,29,37,39,41,42,44,49
Treadmill	8	32	31,32,38,43,48,51,52,54
Exercise in water	1	4	30
Cycle ergometer + treadmill + arm ergometer/stepper	2	8	25,53
Mixed (functional training, treadmill, cycling)	4	16	33,40,45,50
Aerobic exercise time per session (minutes)			
1-10	0	0	
11-20	1	4	27
21-30	11	44	24,26,29-31,33,37,39-42
31-40	6	24	25,32,38,43,51,52
41-50	3	12	44,45,54
51-60	3	12	49,50,53
>60	0	0	
Others	1	4	48†
Number of exercise sessions per week			
1-2	1	4	42
3-5	24	96	24-41,43-54
>5	0	0	
Duration of exercise programme (weeks)			
1-2	0	0	
3-4	4	13	37,48-50
5-6	2	8	31,53
7-8	4	16	27,30,39,44
9-10	3	12	24,25,42
11-12	3	12	26,40,41
13-16	2	8	29,54
>16	7	28	32,33,38,43,45,51,52
Aerobic exercise Intensity			
Low (20-39%HRR, 50-63%HRmax)	1	4	37
Moderate (40-59%HRR, 64-76% HRmax)	7	28	25,26,31,41,45,49,53
High (60-84%HRR, 77-93%HRmax)	16	64	24,27,30,32,33,38,39,40‡,42-44,48,50-52,54
Interval type (Periods of high intensity interspersed with low intensity)	1	4	29

*HRmax = maximal heart rate; HRR = heart rate reserve

†Moore et al [48]: average number of steps taken was 3896 steps per session.

‡Mead et al [40]: The target intensity was set using the rate of perceived exertion of 13-16 according to the Borg scale

Table 3. Practical suggestions for clinical programming

	Practical suggestions
Patient screening	• The medical record should be reviewed to identify health problems that may limit the ability to engage in aerobic training. • The American College of Sports Medicine (ACSM) criteria can be used for cardiac screening [12]. • Cardiac screening using a maximal exercise test with electrocardiographic and blood pressure monitoring is required.
Setting	• Higher-risk individuals or those with acute stroke: supervised training in clinical setting. • Lower-risk individuals (e.g., chronic stroke patients who are medically stable): supervised training in community or individual's own home.
Training modality	• Treadmill, cycle erogmeter, or functional activities (e.g., brisk overground walking, sit-to-stand). • Body weight support may be provided during treadmill training.
Intensity	• Initially: 40-50% HRR (or lower for extremely deconditioned individuals) • Final target: 60-80%HRR. • A heart rate monitor should be worn. • Sporadic blood pressure monitoring is recommended.
Frequency	• 3 to 5 days per week.
Duration	• 20-40 minutes of continuous exercise per session. • Initially, may use short exercise bouts (e.g., 2 minutes), with interspersed rest periods [27,39]. • Longer periods of continuous exercise with shorter rest periods should be used as exercise endurance improves.
Assessment of treatment effect	• Peak VO_2 • Six Minute Walk Test • Maximal walking speed • Activity and participation: e.g., FIM motor score • quality of life measures : e.g., Nottingham Health Profile

.

*FIM=Functional Independence Measure; HRR=heart rate reserve; VO_2=oxygen consumption rate

Figure 1

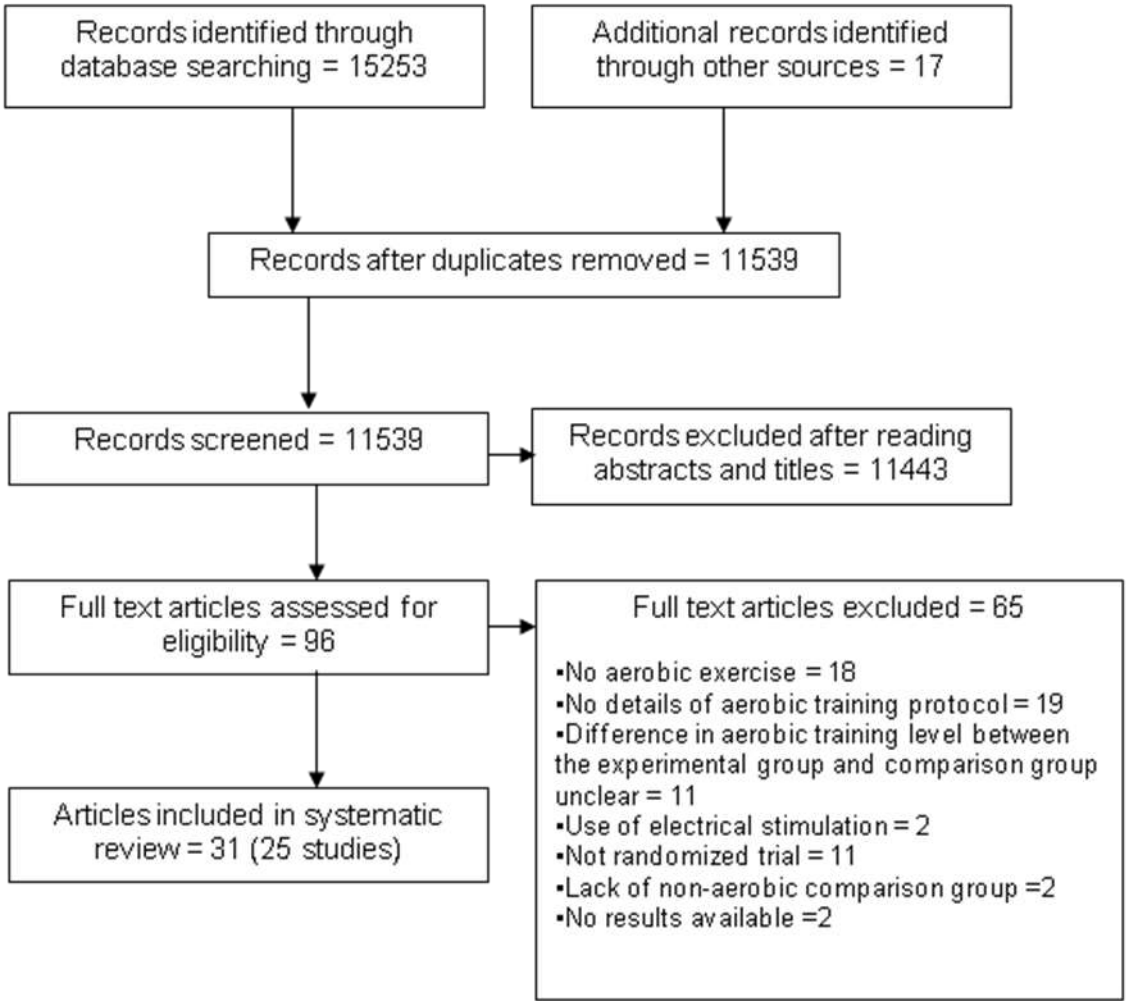
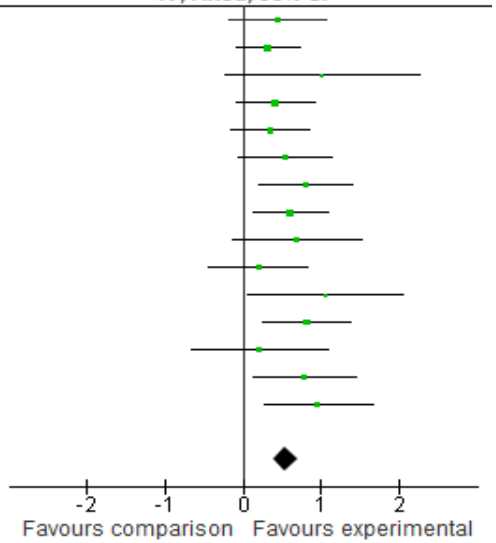

Records identified through database searching = 15253
Additional records identified through other sources = 17
Records after duplicates removed = 11539
Records screened = 11539
Records excluded after reading abstracts and titles = 11443
Full text articles assessed for eligibility = 96
Full text articles excluded = 65
•No aerobic exercise = 18
•No details of aerobic training protocol = 19
•Difference in aerobic training level between the experimental group and comparison group unclear = 11
•Use of electrical stimulation = 2
•Not randomized trial = 11
•Lack of non-aerobic comparison group =2
•No results available =2
Articles included in systematic review = 31 (25 studies)

Figure 2

A.

Study or Subgroup	Experimental group Mean	SD	Total	Comparison group Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Potempa 1995	2.2	4.36	19	0.1	4.79	23	6.5%	0.45 [-0.17, 1.06]	1995
Duncan 2003	1.05	3.3	44	0.06	2.9	48	14.5%	0.32 [-0.09, 0.73]	2003
Chu 2004	3.9	3	7	0.5	3.2	5	1.6%	1.02 [-0.23, 2.27]	2004
Macko 2005	2.4	5.1	32	0.2	5.4	29	9.5%	0.41 [-0.09, 0.92]	2005
Pang 2005	2	5.2	32	0.3	4.3	31	9.9%	0.35 [-0.15, 0.85]	2005
Ivey 2007	2	4.59	26	-0.4	4.02	20	6.9%	0.54 [-0.05, 1.14]	2007
Lennon 2008	1.4	1.6	23	0	1.8	23	6.7%	0.81 [0.20, 1.41]	2008
Luft 2008	2.3	4.34	37	-0.4	4.46	34	10.8%	0.61 [0.13, 1.08]	2008
Lee 2008	1.85	3.86	12	-0.8	3.5	12	3.6%	0.69 [-0.13, 1.52]	2008
Quaney 2009	0.71	4.23	19	-0.28	5.42	19	6.0%	0.20 [-0.44, 0.84]	2009
Letombe 2010	2.26	1.21	9	0.75	1.5	9	2.4%	1.06 [0.05, 2.06]	2010
Ivey 2010	2.5	4	29	-0.7	3.6	24	7.7%	0.82 [0.26, 1.39]	2010
Moore 2010	1	3.2	10	0	5.4	10	3.2%	0.22 [-0.66, 1.10]	2010
Ivey 2011	2.8	4.9	19	-0.7	3.7	19	5.6%	0.79 [0.13, 1.45]	2011
Globas 2012	5.5	4.6	18	-0.8	7.8	18	5.1%	0.96 [0.27, 1.66]	2012
Total (95% CI)			**336**			**324**	**100.0%**	**0.55 [0.39, 0.71]**	

Heterogeneity: Chi² = 9.09, df = 14 (P = 0.83); I² = 0%
Test for overall effect: Z = 6.86 (P < 0.00001)



B.

Study or Subgroup	Experimental group Mean	SD	Total	Comparison group Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Chu 2004	3.9	3	7	0.5	3.2	5	3.8%	1.02 [-0.23, 2.27]	2004
Macko 2005	2.4	5.1	32	0.2	5.4	29	23.0%	0.41 [-0.09, 0.92]	2005
Lee 2008	1.5	4.5	12	-0.8	3.5	12	8.9%	0.55 [-0.27, 1.37]	2008
Lennon 2008	1.4	1.6	23	0	1.8	23	16.3%	0.81 [0.20, 1.41]	2008
Quaney 2009	0.71	4.23	19	-0.28	5.42	19	14.6%	0.20 [-0.44, 0.84]	2009
Moore 2010	1	3.2	10	0	5.4	10	7.7%	0.22 [-0.66, 1.10]	2010
Ivey 2011	2.8	4.9	19	-0.7	3.7	19	13.5%	0.79 [0.13, 1.45]	2011
Globas 2012	5.5	4.6	18	-0.8	7.8	18	12.3%	0.96 [0.27, 1.66]	2012
Total (95% CI)			**140**			**135**	**100.0%**	**0.58 [0.34, 0.83]**	

Heterogeneity: Chi² = 5.01, df = 7 (P = 0.66); I² = 0%
Test for overall effect: Z = 4.71 (P < 0.00001)

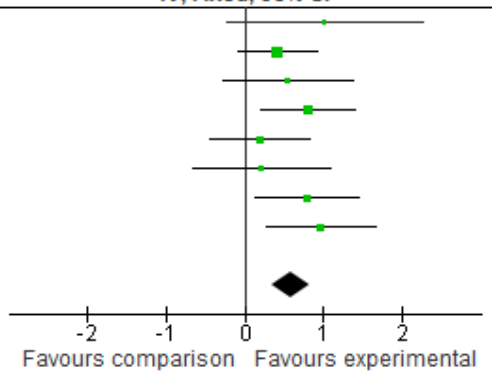


Figure 3

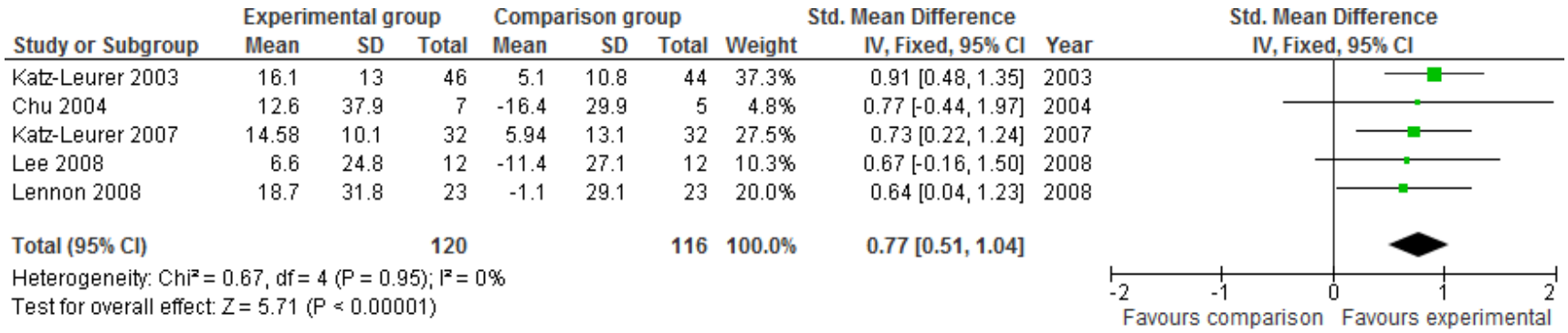
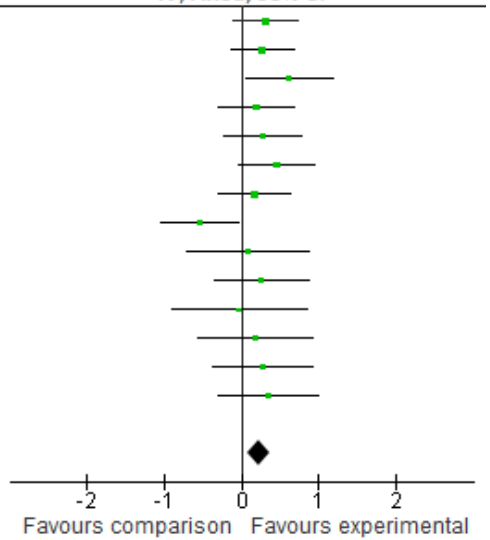

Experimental group
Comparison group
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI Year
IV, Fixed, 95% CI
Katz-Leurer 2003 16.1 13 46 5.1 10.8 44 37.3% 0.91 [0.48, 1.35] 2003
Chu 2004 12.6 37.9 7 -16.4 29.9 5 4.8% 0.77 [-0.44, 1.97] 2004
Katz-Leurer 2007 14.58 10.1 32 5.94 13.1 32 27.5% 0.73 [0.22, 1.24] 2007
Lee 2008 6.6 24.8 12 -11.4 27.1 12 10.3% 0.67 [-0.16, 1.50] 2008
Lennon 2008 18.7 31.8 23 -1.1 29.1 23 20.0% 0.64 [0.04, 1.23] 2008
Total (95% CI) 120 116 100.0% 0.77 [0.51, 1.04]
Heterogeneity: Chi² = 0.67, df = 4 (P = 0.95); I² = 0%
Test for overall effect: Z = 5.71 (P < 0.00001)
-2
-1
0
1
2
Favours comparison
Favours experimental

Figure 4

A.

Study or Subgroup	Experimental group Mean	SD	Total	Comparison group Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Katz-Leurer 2003	143	122.8	46	107.6	94.8	44	12.1%	0.32 [-0.10, 0.74]	2003
Duncan 2003	61.61	103.9	44	33.59	94.8	48	12.4%	0.28 [-0.13, 0.69]	2003
Eich 2004	90.6	50.8	25	55.7	60.1	25	6.5%	0.62 [0.05, 1.19]	2004
Pang 2005	64.6	143.5	32	38.3	123.8	31	8.6%	0.19 [-0.30, 0.69]	2005
Macko 2005	161	412.9	32	20	586.4	29	8.2%	0.28 [-0.23, 0.78]	2005
Katz-Leurer 2007	148.84	127.47	32	98.69	83.88	32	8.5%	0.46 [-0.04, 0.96]	2007
Luft 2008	0.08	0.31	37	0.02	0.36	34	9.7%	0.18 [-0.29, 0.64]	2008
Langhammer 2008	148	211.1	32	258	197.8	31	8.3%	-0.53 [-1.03, -0.03]	2008
Lee 2008	18.2	141.97	12	4.9	162.1	12	3.3%	0.08 [-0.72, 0.88]	2008
Outermans 2010	58.9	145.8	22	21.4	131.5	21	5.8%	0.26 [-0.34, 0.87]	2010
Moore 2010	39	231	10	46	228	10	2.7%	-0.03 [-0.91, 0.85]	2010
Toledano-Zarhi 2011	53.3	172.5	14	24.9	116.3	14	3.8%	0.19 [-0.56, 0.93]	2011
Ivey 2011	127	385	19	25	345	19	5.1%	0.27 [-0.37, 0.91]	2011
Globas 2012	57.7	113	18	4.7	177	18	4.8%	0.35 [-0.31, 1.01]	2012
Total (95% CI)			**375**			**368**	**100.0%**	**0.22 [0.08, 0.37]**	

Heterogeneity: Chi² = 12.34, df = 13 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.98 (P = 0.003)



B.

Study or Subgroup	Experimental group Mean	SD	Total	Comparison group Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Katz-Leurer 2003	143	122.8	46	107.6	94.8	44	19.9%	0.32 [-0.10, 0.74]	2003
Eich 2004	90.6	50.8	25	55.7	60.1	25	10.7%	0.62 [0.05, 1.19]	2004
Macko 2005	161	412.9	32	20	586.4	29	13.5%	0.28 [-0.23, 0.78]	2005
Katz-Leurer 2007	148.84	127.47	32	98.69	83.88	32	13.9%	0.46 [-0.04, 0.96]	2007
Luft 2008	0.08	0.31	37	0.02	0.36	34	15.8%	0.18 [-0.29, 0.64]	2008
Lee 2008	12.2	158.3	12	4.9	162.1	12	5.4%	0.04 [-0.76, 0.84]	2008
Moore 2010	39	231	10	46	228	10	4.5%	-0.03 [-0.91, 0.85]	2010
Ivey 2011	127	385	19	25	345	19	8.4%	0.27 [-0.37, 0.91]	2011
Globas 2012	57.7	113	18	4.7	177	18	7.9%	0.35 [-0.31, 1.01]	2012
Total (95% CI)			**231**			**223**	**100.0%**	**0.31 [0.12, 0.50]**	

Heterogeneity: Chi² = 2.82, df = 8 (P = 0.94); I² = 0%
Test for overall effect: Z = 3.28 (P = 0.001)

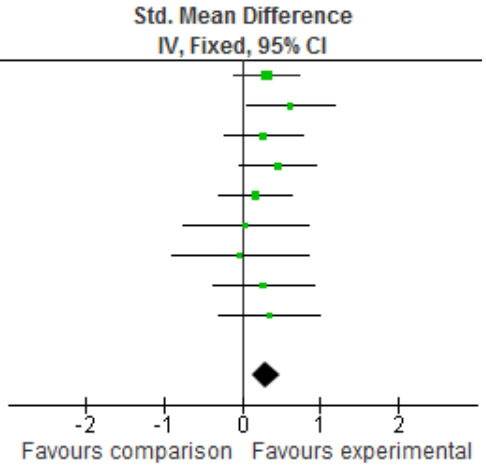
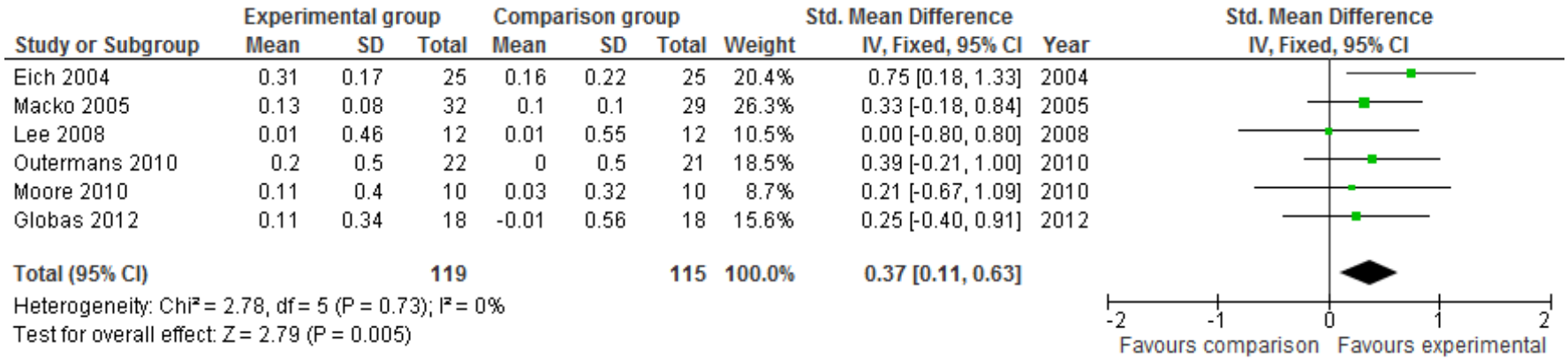


Figure 5


Experimental group
Comparison group
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI Year
IV, Fixed, 95% CI
Eich 2004 0.31 0.17 25 0.16 0.22 25 20.4% 0.75 [0.18, 1.33] 2004
Macko 2005 0.13 0.08 32 0.1 0.1 29 26.3% 0.33 [-0.18, 0.84] 2005
Lee 2008 0.01 0.46 12 0.01 0.55 12 10.5% 0.00 [-0.80, 0.80] 2008
Outermans 2010 0.2 0.5 22 0 0.5 21 18.5% 0.39 [-0.21, 1.00] 2010
Moore 2010 0.11 0.4 10 0.03 0.32 10 8.7% 0.21 [-0.67, 1.09] 2010
Globas 2012 0.11 0.34 18 -0.01 0.56 18 15.6% 0.25 [-0.40, 0.91] 2012
Total (95% CI) 119 115 100.0% 0.37 [0.11, 0.63]
Heterogeneity: Chi² = 2.78, df = 5 (P = 0.73); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)
-2
-1
0
1
2
Favours comparison
Favours experimental