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Factors Influencing the Efficacy of Aerobic Exercise for Improving Fitness and Walking Capacity After Stroke: A Meta-Analysis with Meta-Regression

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Abstract

Objective—To assess the influence of dosing parameters and patient characteristics on the efficacy of aerobic exercise (AEX) post-stroke.

Data Sources—A systematic review was conducted using Pubmed, MEDLINE, CINAHL, PEDro and Academic Search Complete.

Study Selection—Studies were selected that compared AEX to a non-aerobic control group among ambulatory persons with stroke.

Data Extraction—Extracted outcome data included: peak oxygen consumption during exercise testing (VO_{2peak}), walking speed and walking endurance (6-minute walk test). Independent variables of interest were: AEX mode (seated or walking), AEX intensity (moderate or vigorous), AEX volume (total hours), stroke chronicity and baseline outcome scores.

Data Synthesis—Significant between-study heterogeneity was confirmed for all outcomes. Pooled AEX effect size estimates (AEX change – control change) from random effects models were: VO_{2peak} , 2.2 mL/kg/min [95% CI: 1.3, 3.1]; walking speed, 0.06 m/s [95% CI: 0.01, 0.11]; and 6-minute walk test distance, 29 m [95% CI: 15, 42]. From meta-regression, greater VO_{2peak} effect sizes were significantly associated with higher AEX intensity and higher baseline VO_{2peak} . Greater effect sizes for walking speed and the 6-minute walk test were significantly associated with a walking AEX mode. In contrast, seated AEX did not have a significant effect on walking outcomes.

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Conclusions—AEX significantly improves aerobic capacity post-stroke, but may need to be task specific to impact walking speed and endurance. Higher AEX intensity is associated with better outcomes. Future randomized studies are needed to confirm these results.

Keywords

stroke; exercise; deconditioning; locomotion; aerobic; dosing

MAIN MANUSCRIPT

The majority of persons who survive a stroke eventually regain the ability to walk without continuous physical assistance from another person,^{1,2} but less than 10% achieve adequate walking speed and endurance to resume independent living and normal community participation.³ This limited walking capacity is primarily attributable to impaired motor control.^{4–10} However, aerobic deconditioning is very common after stroke¹¹ and may also contribute to walking limitations, especially in relation to endurance.^{4–10,12} Therefore, aerobic exercise (AEX) is recommended after stroke to improve both aerobic conditioning and walking capacity.¹¹

However, the effect of post-stroke AEX on aerobic capacity and walking function appears to be highly variable. For example, aerobic capacity effect sizes in previous studies (AEX group change minus control group change) have ranged from -1.5^{13} to $+6.3^{14}$ mL/kg/min, walking speed effect sizes have ranged from -0.09^{15} to $+0.25^{16}$ m/s and walking endurance (6-minute walk test) effect sizes have ranged from -25^{17} to $+89^{16}$ m. An understanding of the factors affecting these between study differences could help inform AEX prescription and prioritize future studies.

Meta-regression is a meta-analysis technique that uses regression methods to assess the effect of different factors on study effect sizes.^{18,19} It is plausible that AEX mode, AEX intensity, AEX volume, stroke chronicity and baseline function would be key factors that influence AEX effect sizes post-stroke.^{20,21} For example, neuroplasticity principles indicate that training effectiveness is largely determined by the task-specificity (mode), intensity and repetition (volume) of practice.^{21,22} On the other hand, it has been suggested that AEX could improve walking speed and endurance after stroke, regardless of task-specificity (AEX mode).^{23–27} Several of the above factors that could moderate AEX effect sizes (AEX mode, AEX intensity and baseline function) have not been previously assessed with meta-regression. Therefore, the purpose of this meta-analysis was to assess the influence of AEX dosing parameters and patient characteristics on the efficacy of AEX for improving aerobic fitness and walking function after stroke.

Methods

Search Strategy

Studies were identified by searching electronic databases and scanning reference lists of articles in October and November of 2015. The database search included Pubmed, MEDLINE, Cumulative Index of Nursing and Allied Health Literature (CINAHL),

Physiotherapy Evidence Database (PEDro), and Academic Search Complete. The following search terms were used: stroke, cerebrovascular accident, cva, hemipleg*, hemipar*, aerobic, fitness, endurance, cardio, cardiovascular, exercis*, train*, protocol*, program*, conditioning (see appendix for full search strategy).

Eligibility Criteria

Types of studies—Studies comparing AEX to a non-aerobic control group among persons with a history of stroke. Full text reports had to be available in English so that AEX intervention could be confirmed and independent variables of interest could be extracted. No publication status or publication date restrictions were imposed. When it could not be determined whether study data were redundant with a previous publication, only the most recent report with all needed variables was used.

Types of participants—Adult humans with a history of stroke, who were able to walk without continuous physical assistance from another person (assistive devices, orthotics and guarding were allowed). No restrictions were imposed based on stroke characteristics or chronicity.

Types of interventions—AEX was defined as any activity involving the repetitive activation of large muscle groups with a target or actual aerobic intensity above 39% heart rate reserve (HRR), peak oxygen consumption rate (VO_{2peak}) or peak work rate, or above 63% maximal heart rate (HR_{max}).^{28,29} Studies (or intervention groups within studies) were excluded if they tested the combined effects of aerobic and strength training.

Types of outcome measures—1) VO_{2peak} from graded exercise testing; 2) comfortable or fastest walking speed over a short distance (e.g. 10m walk test); or 3) a timed walking distance test (e.g. 6-minute walk test). Only change scores from baseline to immediately post-intervention were included, because longer-term follow up scores were not available in most studies.

Quality Assessment and Data Extraction

The primary author assessed study eligibility and study quality and extracted study data into a spreadsheet. Study quality was assessed with the PEDro scale, yielding a score from 0 (lowest quality) to 10 (highest quality), but study quality was not used as a determinant of eligibility. Information was extracted from each included trial on: 1) study design and eligibility criteria; 2) characteristics of trial participants, including mean age, time post stroke (classified as subacute [< 6 months] or chronic [≥ 6 months]), and mean baseline outcome variables of interest; 3) characteristics of the AEX intervention, including the AEX mode (classified as seated or walking), mean AEX intensity (classified as moderate or vigorous),^{28,29} and total AEX volume in hours (calculated by hours/session $\times$ sessions/week $\times$ total weeks); and 4) outcomes, including mean changes and standard deviations in each group, effect sizes (mean differences), corresponding variances and whether exercise tests for assessing VO_{2peak} were maximal (symptom-limited) or submaximal (terminated at a target HR). When mean AEX intensity was not reported, it was estimated from data provided, including peak AEX intensity, starting AEX intensity target and final AEX

intensity target. Moderate AEX intensity was defined as 40–59% HRR or VO_{2peak} or 64–76% HR_{max} .^{28,29} Vigorous AEX intensity was defined as 60–84% HRR or VO_{2peak} or 77–93% HR_{max} .^{28,29}

For outcomes, effect sizes were calculated as the mean change (immediate post intervention minus baseline) in the AEX group minus mean change in control group ($\bar{X}_a - \bar{X}_b$), or equivalently by taking the regression coefficient for the appropriate group by time interaction. Variances were calculated using the following formulas,

$$Var(\bar{X}_{a\Delta} - \bar{X}_{b\Delta}) = \frac{\hat{\sigma}_{\Delta}^2}{n_a} + \frac{\hat{\sigma}_{\Delta}^2}{n_b} \quad (1)$$

$$\hat{\sigma}_{\Delta}^2 = \frac{(n_a - 1)\hat{\sigma}_{a\Delta}^2 + (n_b - 1)\hat{\sigma}_{b\Delta}^2}{n_a + n_b - 2} \quad (2)$$

where $\hat{\sigma}_{\Delta}^2$ is the pooled standard deviation of change, $\hat{\sigma}_{a\Delta}^2$ and $\hat{\sigma}_{b\Delta}^2$ are the standard deviations of change in the AEX and control groups, respectively, and n_a and n_b are the group sample sizes. When standard deviations of change were not provided, but p values were available, $\hat{\sigma}_{\Delta}^2$ was calculated by obtaining the t score corresponding to the reported p value and degrees of freedom, and using the formula,

$$\hat{\sigma}_{\Delta}^2 = \left(\frac{(\bar{X}_{a\Delta} - \bar{X}_{b\Delta}) \times \sqrt{n_a + n_b}}{2t} \right)^2 \quad (3)$$

When exact p values were not available (e.g. $p < 0.01$), the highest possible p value with one additional digit (e.g. $p = 0.009$) was used for the variance calculation, to reflect the uncertainty. When neither standard deviations of change nor needed p values were provided, the within group standard deviations of change ($\hat{\sigma}_{a\Delta}^2$ and $\hat{\sigma}_{b\Delta}^2$) were estimated using the formulas,

$$\sigma_{a\Delta}^2 = \sigma_{a0}^2 + \sigma_{a1}^2 - (2r\sigma_{a0}\sigma_{a1}) \quad (4)$$

$$\sigma_{b\Delta}^2 = \sigma_{b0}^2 + \sigma_{b1}^2 - (2r\sigma_{b0}\sigma_{b1}) \quad (5)$$

where the subscripts 0 and 1 represent the baseline and post intervention time points and r is the within-subject repeated measures correlation. This correlation was estimated by

averaging values calculated from other studies that reported sufficient data. These within group standard deviation of change estimates were then used to calculate $\hat{\sigma}_{\Delta}^2$ using formula (2) above.

Statistical Methods

Between study heterogeneity was assessed with Cochran's Q , I^2 and random effects model estimates of the between study standard deviation. The overall meta-analysis for each dependent variable (VO_{2peak} , walking speed and 6-minute walk test) calculated a pooled effect size estimate across all eligible studies, using a random effects model. Meta-regression models were then conducted to assess the association between study effect size and each independent variable of interest (AEX mode, AEX intensity, AEX volume, stroke chronicity and baseline level of the dependent variable).

For dichotomous independent variables (AEX mode, AEX intensity, stroke chronicity), pooled effect size estimates were obtained for both levels of the independent variable (e.g. seated and walking AEX mode) and for the difference between levels (e.g. walking mode minus seated mode). For continuous independent variables (AEX volume, baseline level of the dependent variable), pooled effect size estimates were obtained at the mean level of the independent variable (e.g. mean AEX volume across studies) and for every unit increase in the independent variable (e.g. every 10 hour increase in AEX volume). There were an insufficient number of studies to model more than one independent variable at a time.

Meta-regression models treated the independent variable of interest as a fixed factor and included a random effect for study. In cases where multiple effect sizes were included from the same study, an additional random effect was added to account for within-study correlation. For example, one study¹⁴ included both a parallel group design and a control group crossover. For walking speed, several studies included separate comparisons for both comfortable and fast speed. It was determined *a priori* that these two types of walking speed tests would be pooled together if walking speed type did not significantly affect the pooled effect size estimate and there were no statistically significant interactions between walking speed type and any of the independent variables.

Publication bias was visually assessed with funnel plots and two sensitivity analyses were performed to assess the robustness of study findings. The first sensitivity analysis concerned uncertainty about the best way to represent AEX volume in the meta-regression. Each of the components contributing to AEX volume (minutes/session, sessions/week and total weeks) was tested separately as an independent variable for each outcome. The second sensitivity analysis concerned uncertainties about data extraction. For studies where exact p-values were not available and conservative estimates were used to calculate variance (e.g. $p < 0.01$ to $p = 0.009$), the effect of using p values at the next lower level of significance (e.g. 0.009 to 0.001) was tested. For studies where within-subject repeated measures correlations had to be estimated from other studies, the effect of a wide range of possible correlations (0.50 to 0.99) was tested.

The third sensitivity analysis concerned a limitation to conventional statistical models used for meta-analysis. Because random effects models treat the maximum likelihood estimate for

between study variance as a known parameter value and do not account for its uncertainty, they may underestimate the standard error and width of confidence intervals on parameters of interest. Therefore, Bayesian models using Markov Chain Monte Carlo simulation were conducted to test the robustness of any significant findings when accounting for the uncertainty associated with the estimation of between study variance. These models were constructed to match the variables in the corresponding random effects models. Vague prior distributions were used for the parameters of interest (normal distribution with mean 0 and SD 1000) and the inverse variance estimates (gamma distribution with shape 0.001 and rate 0.001). Each model included 4 chains and achieved convergence with 100,000 total saved iterations after a burn-in period of 50,000 iterations per chain.

An additional benefit of these Bayesian models is that they provide novel results that can facilitate interpretation. Whereas conventional frequentist p values indicate the probability of obtaining the given data if the null hypothesis were true, Bayesian posterior probabilities indicate the probability of the alternative hypothesis being true after combining the data with any prior knowledge. In this study, vague prior distributions (no prior assumptions) were used to allow the data to drive the models. Posterior probabilities were calculated to determine the probability of an association between the independent variable and the effect size, and to determine the probability that a particular level of the independent variable has an effect size >0. These probabilities were obtained by calculating the percentage of simulation iterations that resulted in a regression coefficient >0 for the parameters of interest.

SAS (version 9.4) was used for the random effects models. WinBUGS (version 1.4.3),³⁰ R (version 3.0.0)³¹ and the R2WinBUGS package³² were used for the Bayesian models. The significance level was set at 0.05.

Results

Twenty studies were found that met eligibility criteria for inclusion in the meta-analyses (Figure 1 and Table 1). There were 15 studies (598 participants) for VO_{2peak} , 13 studies (415 participants) for walking speed and 16 studies (734 participants) for the 6-minute walk test. Mean stroke chronicity ranged from 0.4 to 70.0 months; baseline comfortable walking speed ranged from 0.34 to 1.00 m/s; and study quality ranged from 3 to 8 out of 10 on the PEDro scale (Table 1). The 27 studies that did not meet eligibility criteria after full text review are listed in the appendix.

VO_{2peak}

For VO_{2peak} , there were 16 effect sizes reported among the 15 studies (one study¹⁴ gave both parallel group and crossover comparisons). As shown on the first row of Table 2, the overall meta-analysis calculated a pooled effect size (AEX change – control change) of 2.2 mL/kg/min [95% CI: 1.3, 3.1]. Significant between-study heterogeneity was confirmed by the model estimate of the between study standard deviation (1.3 mL/kg/min, 95% CI: 0.8, 3.0) and the Cochran's Q statistic ($p < .0001$). I^2 indicated that between study variability comprised 67% of the total variability.

The remaining rows under VO_{2peak} in Table 2 show the results of the meta-regression models. AEX intensity and baseline VO_{2peak} were the only independent variables significantly associated with VO_{2peak} effect size (see confidence intervals for the comparison – reference column). Adding AEX intensity to the overall model dropped the I^2 from 67% to 37% and made the Cochran's Q estimate of between study heterogeneity non-significant. The effect size [95% CI] for moderate intensity was 1.6 [0.8, 2.4] mL/kg/min, whereas vigorous intensity was 3.8 [2.4, 5.2] mL/kg/min and the difference between vigorous and moderate intensity was 2.2 [0.6, 3.9] mL/kg/min. Figure 2 shows a forest plot of VO_{2peak} effect sizes, grouped by AEX intensity. Mean baseline VO_{2peak} across studies was 14.6 mL/kg/min. At this level, the VO_{2peak} effect size was 2.2 [1.5, 2.9], which matched the overall meta-analysis pooled effect size, but with a narrower confidence interval. For every 1 mL/kg/min increase in baseline VO_{2peak} , the VO_{2peak} effect size increased by 0.4 [0.1, 0.6] mL/kg/min. The VO_{2peak} effect size was not significantly different between submaximal and maximal exercise tests. However, the effect size estimate was significantly greater than zero for studies using a maximal test, but not for studies using a submaximal test.

Walking speed

For walking speed, there were 23 effect sizes reported among the 13 studies (one study¹⁴ gave both parallel group and crossover comparisons and 8 studies [including¹⁴] reported data on both fast and comfortable walking speed). Walking speed type (fast vs comfortable) did not significantly affect the walking speed mean difference ($p=0.18$, see the 2nd row under walking speed in Table 2) and there were no statistically significant interactions between walking speed type and any of the meta-regression independent variables (all $p > 0.55$). Therefore, comfortable and fast walking speeds were pooled together for analysis. The overall meta-analysis calculated a pooled effect size of 0.06 [0.01, 0.11] m/s. Significant between-study heterogeneity was again observed and I^2 indicated that between study variability comprised 78% of the total variability. In meta-regression, AEX mode was the only independent variable significantly associated with walking speed effect size. The effect size for seated AEX mode was -0.05 [-0.14, 0.05] m/s, whereas walking AEX mode was 0.09 [0.04, 0.13] m/s and the difference between walking and seated mode was 0.13 [0.03, 0.24] m/s. Figure 3 shows a forest plot of walking speed effect sizes, grouped by AEX mode. Although the walking speed effect size was not significantly different between the comparison and reference levels of the remaining independent variables, the effect size was not significantly different from zero for comfortable walking speed, moderate AEX intensity, or chronic stroke.

Six-minute walk test

For the 6-minute walk test, there were 17 effect sizes reported among the 16 studies (one study¹⁴ gave both parallel group and crossover comparisons). The overall meta-analysis calculated a pooled effect size of 29 [15, 42] m. Significant between-study heterogeneity was again observed and I^2 indicated that between study variability comprised 79% of the total variability. In meta-regression, AEX mode was the only independent variable significantly associated with 6-minute walk test effect size. Adding AEX mode to the overall model dropped the I^2 from 79% to 23% and made the Cochran's Q estimate of between study heterogeneity non-significant. The effect size for seated AEX mode was 4 [-11, 19]

m, whereas walking AEX mode was 38 [27, 50] m and the difference between walking and seated mode was 34 [15, 53] m. Figure 4 shows a forest plot of 6-minute walk test effect sizes, grouped by AEX mode.

Sensitivity analyses and Bayesian posterior probabilities

In the sensitivity analysis testing different ways of decomposing AEX volume for each outcome, the only significant result was that longer session duration was associated with lower 6-minute walk test effect sizes, with a slope of -16 [-29 , -3] m per 10 minute increase (Table 3). In the data extraction sensitivity analysis, the significance of the primary meta-regression results was not affected by the use of less conservative p values or different within subject repeated measures correlations for uncertain variance calculations (Table 4). In the third sensitivity analysis, Bayesian models (Table 5) also gave similar results to the significant random effects models. For VO_{2peak} , these Bayesian models estimated a 99.7% probability that vigorous AEX intensity is associated with greater effect size than moderate AEX intensity. The probability that higher baseline VO_{2peak} is associated with greater VO_{2peak} effect size was also 99.7%. For walking speed and the 6-minute walk test, the Bayesian models gave probabilities $>99\%$ that walking AEX mode is associated with greater effect size than seated AEX mode. For the subgroup of studies using a seated AEX mode, the probabilities of an effect size >0 for walking speed and the 6-minute walk test were 16% and 94% respectively. These probabilities were $>99.9\%$ for the subgroup of studies using a walking AEX mode. Funnel plots did not show any gross asymmetry (Figure 5).

Discussion

This meta-analysis estimated the following overall pooled AEX effect sizes (AEX change minus control change): VO_{2peak} , 2.2 mL/kg/min [95% CI: 1.3, 3.1]; walking speed, 0.06 m/s [95% CI: 0.01, 0.11]; 6-minute walk test distance, 29 m [95% CI: 15, 42]. From meta-regression analysis for VO_{2peak} , higher AEX intensity (vigorous vs. moderate) and higher baseline VO_{2peak} were significantly associated with greater effect sizes. For walking speed and the 6-minute walk test, a more task specific mode of AEX (walking vs. seated) was significantly associated with greater effect sizes.

Similar to previous meta-analyses on this topic,^{24–27,48,49} the overall pooled effect size estimates and 95% confidence intervals from this study confirmed that post-stroke AEX has a significant positive effect on aerobic capacity, walking speed and walking endurance. Clinically important difference (CID) thresholds for these outcomes have been estimated at 1.0–3.0 mL/kg/min for VO_{2peak} ,^{50–52} 0.05–0.20 m/s for walking speed,^{53–58} and 20–50 m for the 6-minute walk test.^{58,59} Thus, on average, AEX appears to have at least some clinically meaningful impact on these outcomes.

However, the current meta-regression results show that these benefits may not occur with all types of AEX and all types of patients. For example, effect size estimates for walking speed and the 6-minute walk test were not significantly different from zero for studies which used a seated AEX mode (e.g. cycle) and the 95% confidence intervals excluded the possibility of a meaningful effect, with upper bounds of 0.046 m/s and 19 m. Thus, while seated AEX significantly improves aerobic capacity, it would not be expected (on average) to have a

meaningful impact on walking speed or walking endurance post-stroke. This finding is especially noteworthy because it contradicts the current view that cardiovascular conditioning alone improves walking function post-stroke.^{23–27} This view appears to be largely based on cross sectional studies that indicate an association between aerobic capacity and walking function.²³ However, these studies did not control for motor function^{4–10,12} and many also indicated that motor function (not aerobic capacity) was the primary determinant of walking speed and endurance. Given the importance of task-specific training for improving motor function^{21,22} and the results of this meta-analysis, it appears that AEX may need to be task-specific (i.e. use a walking mode) to meaningfully impact walking function for persons who are ambulatory post-stroke.

The meta-regression results also provide guidance on other aspects of AEX dosing and patient selection. For moderate intensity AEX, effect sizes were significant for aerobic capacity and walking endurance, but not walking speed. In contrast, the effect sizes for vigorous intensity were significant for all outcomes and were significantly greater than moderate intensity for aerobic capacity. Thus, vigorous AEX appears to be more efficacious than moderate intensity AEX post-stroke, which is consistent with a recent randomized controlled trial.⁶⁰ Higher baseline VO_{2peak} was associated with greater VO_{2peak} effect sizes, but baseline walking function was not a significant predictor for the walking outcomes. Overall AEX volume and stroke chronicity did not significantly influence any outcome. However, the effect of stroke chronicity on walking speed and 6-minute walk test effect sizes was at least somewhat clinically meaningful and nearly statistically significant (confidence intervals barely crossing zero) favoring the subgroup of studies that involved participants < 6 months post-stroke. In addition, the effect size for walking speed was only significant in this subacute subgroup. Thus, AEX appears to meaningfully improve VO_{2peak} and 6-minute walk test distance even in chronic stroke, but earlier intervention in the subacute period may yield greater effects on 6-minute walk distance and may be necessary to improve walking speed with AEX.

Study Strengths and Limitations

The major strength of the current meta-analysis is that it included a large number of studies relative to previous meta-analyses on this topic^{24–27,48,49} and used random effects models with meta-regression to partially explain between-study heterogeneity in change score mean differences. In contrast, previous meta-analyses on AEX post-stroke have been limited by: 1) the use of fixed effects models,^{24,27} which make the untenable assumption of zero between-study heterogeneity; 2) the extraction of differences in post-training means (rather than change scores),⁴⁸ or baseline variability (rather than change variability),²⁷ both of which decrease within study precision; 3) the unnecessary reporting of effect sizes in standard deviation units,^{24–27} which makes clinical interpretation more challenging; and 4) the use of statistical tests on raw effect sizes (rather than meta-regression),²⁷ which does not account for between-trial differences in precision.

Another strength of the current meta-regression is that it assessed the influence of several important independent variables that had not been previously tested, including AEX mode, AEX intensity and baseline function, all of which were significant. Further, the funnel plots

did not raise concerns about publication bias and the results were found to be robust across several sensitivity analyses, including Bayesian models that accounted for the uncertainty associated with the estimation of between study variance. This was the first meta-analysis on post-stroke AEX to use this Bayesian approach. In addition to demonstrating the robustness of the findings from the random effects models, the Bayesian models provided novel data about the probability of greater effect sizes with different levels of the independent variables. These probabilities were all >99% for the factors that were significant in the random effects models.

An important limitation of this meta-regression is that there were insufficient studies to test multiple independent variables simultaneously. This made it impossible to test or control for confounding or interactions between independent variables, thus making causal inferences uncertain. For example, it is likely that longer session duration was associated with lower 6-minute walk test effect sizes because longer session duration is associated with lower intensity. Another limitation to this meta-regression is that all independent variables except AEX mode often have variability at the individual level, but could only be extracted as group averages. Thus, it is possible that the observed associations (or lack thereof) for these independent variables do not apply at the individual level (i.e. ecologic fallacy).¹⁹ An additional limitation to this analysis is that there was some heterogeneity in the quality of included studies (see PEDro scores in Table 1) that could have affected the results in unknown ways. We opted to include studies regardless of quality to avoid the use of an arbitrary cutoff and to provide as many data points as possible for the meta-regression.

It is also important to recognize that this analysis only included studies among persons who could ambulate without continuous physical assistance from another person, which resulted in the exclusion of one study.⁶¹ Therefore, the results may not be applicable to persons who are non-ambulatory or who require greater assistance than can be provided by assistive devices, orthotics and guarding. Another important note is that AEX intensity is not systematically reported in the literature.⁶² Therefore, coding AEX intensity as moderate or vigorous for each study included in this analysis required some inference during data extraction. For example, all 20 studies reported planned intensity, but only 5 studies reported the mean aerobic intensity actually achieved^{14,17,38,41,45} and 4 of these studies (all except¹⁴) reported an actual aerobic intensity that was lower than the planned intensity. Ideally, future studies should report mean HR or time spent above moderate and vigorous intensity thresholds during training sessions,⁶³ as well as any progression of actual aerobic intensity across the training regimen. It also needs to be specified whether training HR is being expressed as a percentage of peak HR from an exercise test or as a percentage of age-predicted HR_{max}, as this is likely to affect training intensity for persons with stroke.⁶⁴ Such reporting would facilitate comparisons between studies and assist with clinical translation.

Future Research Directions

In some stroke rehabilitation settings, seated AEX is more feasible to implement than walking AEX, even for patients who are ambulatory, due to fall risk. However, the meta-regression results indicated that conventional seated AEX is unlikely to elicit meaningful improvements in walking function. Therefore, future studies should test whether other

dosing parameters (e.g. intensity, timing) can be manipulated to improve the effects of seated AEX on walking function. For example, AEX has been shown to acutely increase circulating levels of neurotrophins among healthy adults.⁶⁵ Thus, it has been proposed that AEX in close temporal proximity to task-specific training (i.e. walking practice) might augment the effects of task specific training on motor control improvement (i.e. walking function).⁶⁶ Given the potential confounding and ecologic fallacy pitfalls of meta-regression, further randomized trials are also needed to confirm the significant independent variables found in this analysis. Such trials should also seek to investigate interactions between factors (e.g. intensity and volume).

Conclusions

This meta-regression of AEX studies among ambulatory persons with stroke found that higher aerobic intensity and higher baseline aerobic capacity were significantly associated with greater improvements in aerobic capacity. In contrast to the subgroup of studies that used walking AEX modes, seated AEX studies showed no significant effect on walking speed or endurance. Thus, AEX-related improvements in walking function appear to require task-specific training. Further randomized trials are needed to confirm these meta-regression results.

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ABBREVIATIONS

AEX	aerobic exercise
CINAHL	Cumulative Index of Nursing and Allied Health Literature
HRR	heart rate reserve
HR_{max}	maximal heart rate
PEDro	Physiotherapy Evidence Database
VO_{2peak}	peak oxygen consumption rate

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APPENDIX

Search strategy

1. stroke OR cerebrovascular accident OR cva OR hemipleg* OR hemipar*
2. aerobic OR fitness OR endurance OR cardio OR cardiovascular OR exercis* OR intense OR intensity
3. train* OR protocol* OR program* OR conditioning OR “aerobic exercise” OR “endurance exercise” OR “cardiovascular exercise”
4. 1 AND 2 AND 3

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Figure 1.
PRISMA Flow Diagram

Figure 2. Forest plot of VO₂peak mean differences by AEX intensity

AEX, aerobic exercise; VO₂peak, peak oxygen uptake during graded exercise test; SD, standard deviation; RE, random effects; CI, confidence interval

Figure 3. Forest plot of walking speed mean differences by AEX mode

AEX, aerobic exercise; SD, standard deviation; RE, random effects; CI, confidence interval; CWS, comfortable walking speed; FWS, fast walking speed

Figure 4. Forest plot of 6-minute walk test mean differences by AEX mode
AEX, aerobic exercise; SD, standard deviation; RE, random effects; CI, confidence interval

Figure 5. Funnel plots of mean differences (AEX-control) by study sample size
AEX, aerobic exercise. Dotted lines indicate random effects model estimate for population mean difference

Table 1

Characteristics of Included Studies

First Author/ Year	N	Stroke Chronicity (months)	Design	AEX mode(s)	Control group	AEX Aerobic intensity	Total AEX hours	Baseline VO _{2peak} (mL/kg/min)	Baseline CWS (m/s)	Baseline FWS (m/s)	Baseline 6MWT (m)	PDro score (0–10)
Chu 2004 ³³	12	42.0	RCT	aquatic gait	Seated arm exercise	vigorous	24	17.2	1.00	-	-	6
Eich 2004 ³⁴	50	1.4	RCT	TM (? rail, harness, 0–15% BWS pm)	Conventional PT	vigorous	15	-	-	0.42	109	8
Globas 2012 ¹⁴	36	65.1	RCT	TM (rail pm, no harness)	Conventional PT	vigorous	26	20.3	0.72	0.90	268	7
Globas 2012 ¹⁴ (control crossover)	16	70.0	AB	TM (rail pm, no harness)	Conventional PT	vigorous	26	21.7	0.70	0.88	261	6
Gordon 2013 ³⁵	128	12.3	RCT	OG	Massage	vigorous	18	-	-	-	238	7
Holleran 2015 ¹³	12	35.0	Crossover	TM (? rail, harness, no BWS) + OG	TM - 35% HRR	moderate	8	10.3	0.55	0.67	199	4
Hornby 2015 ¹⁶	32	3.3	RCT	TM (rail pm, harness, BWS pm) + OG	Conventional PT - 35% HRR	vigorous	27	-	0.34	0.47	124	7
Ivey 2011 ³⁶	38	>6	RCT	TM (rail, harness, no BWS)	Stretching	moderate	52	14.1	0.51	-	197	5
Jin 2013 ³⁷	128	18.3	RCT	cycle	Low-intensity OG	moderate	40	13.2	-	-	212	4
Kuys 2011 ³⁸	30	1.7	RCT	TM (rail, no harness)	Conventional PT	moderate	9	-	0.46	0.63	198	8
Lee 2008 ¹⁵ (cycle vs control)	25	59.1	RCT	cycle	Sham AEX	moderate	15	13.3	0.69	0.93	261	8
Lennon 2008 ³⁹	46	55.5	RCT	cycle	Conventional rehab	moderate	8	10.9	-	-	-	7
MacKay-Lyons 2013 ⁴⁰	50	0.8	RCT	TM (rail pm, harness, up to 40% BWS pm)	Conventional PT	vigorous	24	14.4	0.54	-	192	8
Macko 2005 ⁴¹	45	36.9	RCT	TM (? rail, ? harness)	Stretching	moderate	52	14.8	0.65	0.86	244	5
Moore 2010 ⁴²	20	13.0	Crossover	TM (rail, harness, 0–40% BWS pm)	No intervention	moderate	14	16.0	0.56	0.77	192	5
Quaney 2009 ⁴³	38	58.8	RCT	cycle	Stretching	moderate	18	14.7	-	-	-	6
Rimmer 2009 ⁴⁴ (MISD vs control)	36	>6	NRCT	cycle	Stretching, strength, balance	moderate	21	13.4	-	-	-	4
Severinsen 2014 ¹⁷ (AEX vs control)	29	15.1	RCT	cycle	Low-intensity arm strengthening	vigorous	36	16.3	-	0.85	310	5
Tang 2014 ⁴⁵	47	49.8	RCT	cycle + OG + functional	Stretching, balance	moderate	52	16.9	-	-	300	8
Tang 2009 ⁴⁶	36	0.6	Matched	cycle	Conventional rehab	moderate	5	11.4	0.66	1.03	203	3
Toledano-Zarhi 2011 ⁴⁷	28	0.4	RCT	cycle + TM (? rail, ? harness)	Usual care	moderate	9	-	-	-	438	6

AEX, aerobic exercise; VO_{2peak}, peak oxygen consumption during a graded exercise test; CWS, comfortable walking speed; FWS, fast walking speed; RCT, randomized controlled trial; NRCT, Non-randomized controlled trial; TM, treadmill walking; rail, use of treadmill handrail; harness, fall protection harness; BWS, body weight support; pm, pro re nata (as needed); OG, overground walking; cycle, lower body ergometer or seated stepper; PT, physical therapy; HRR, heart rate reserve

Table 2

Summary of Random Effects Meta-Regression Results

Reference		Comparison			Comparison - Reference		Between Study Heterogeneity			
Subgroup/condition	Model Estimate	95% CI	Subgroup/condition	Model Estimate	95% CI	Model Estimate	95% CI	SD Model Estimate	I ²	P value
VO _{2-peak} , mL/kg/min (N=15 studies; n=598 participants)										
All studies	2.2	1.3, 3.1	-	-	-	-	-	1.3	0.8, 3.0	66.5% <.0001
Submaximal GXT	0.9	-1.1, 2.9	Maximal GXT	2.5	1.5, 3.5	1.6	-0.6, 3.8	1.2	0.8, 2.9	61.2% 0.0007
Seated AEX mode	1.7	0.6, 2.8	Walking mode	3.0	1.6, 4.3	1.3	-0.4, 3.0	1.1	0.7, 3.7	50.6% 0.0108
Moderate AEX intensity	1.6	0.8, 2.4	Vigorous intensity	3.8	2.4, 5.2	2.2	0.6, 3.9	0.8	0.5, 4.8	36.6% 0.0710
Mean AEX volume (26 h)	2.2	1.3, 3.1	Every 10 h unit ↑	-	-	0.4	-0.2, 0.9	1.3	0.8, 3.1	59.7% 0.0012
Chronic stroke	2.2	1.2, 3.2	Subacute stroke	2.1	0.6, 3.7	-0.1	-3.2, 2.9	1.4	0.9, 3.1	66.3% <.0001
Mean baseline VO _{2-peak} (14.6 mL/kg/min)	2.2	1.5, 2.9	Every 1 mL/kg/min unit ↑	-	-	0.4	0.1, 0.6	0.8	0.5, 3.1	41.0% 0.0447
Walking Speed, m/s (N=13 studies; n=415 participants [*])										
All studies	0.06	0.01, 0.11	-	-	-	-	-	0.07	0.05, 0.17	77.7% <.0001
Comfortable speed	0.05	-0.01, 0.10	Fast speed	0.08	0.02, 0.13	0.03	-0.01, 0.07	0.08	0.05, 0.18	77.7% <.0001
Seated AEX mode	-0.05	-0.14, 0.05	Walking mode	0.09	0.04, 0.13	0.13	0.03, 0.24	0.06	0.03, 0.15	76.4% <.0001
Moderate AEX intensity	0.03	-0.03, 0.09	Vigorous intensity	0.10	0.03, 0.17	0.07	-0.03, 0.17	0.06	0.05, 0.20	64.6% <.0001
Mean AEX volume (24 h)	0.06	0.01, 0.11	Every 10 h unit ↑	-	-	0.00	-0.04, 0.04	0.08	0.05, 0.19	71.8% <.0001
Chronic stroke	0.03	-0.03, 0.08	Subacute stroke	0.12	0.04, 0.19	0.09	-0.00, 0.18	0.06	0.03, 0.18	70.9% <.0001
Mean baseline walking speed (0.68 m/s)	0.06	0.01, 0.11	Every 0.20 m/s unit ↑	-	-	0.00	-0.04, 0.04	0.08	0.05, 0.29	77.6% <.0001
6-Minute Walk Test Distance, m (N=16 studies; n=734 participants)										
All studies	29	15, 42	-	-	-	-	-	19	12, 46	78.5% <.0001
Seated AEX mode	4	-11, 19	Walking mode	38	27, 50	34	15, 53	9	4, 292	22.9% 0.1882
Moderate AEX intensity	23	6, 40	Vigorous intensity	36	15, 58	13	-14, 41	19	11, 54	60.8% 0.0006
Mean AEX volume (29 h)	28	14, 42	Every 10 h unit ↑	-	-	-4	-12, 5	19	12, 49	70.0% <.0001
Chronic stroke	21	5, 37	Subacute stroke	46	22, 70	25	-4, 53	18	11, 44	70.6% <.0001
Mean baseline 6-minute walk distance (231 m)	29	15, 42	Every 50 m unit ↑	-	-	-5	-14, 4	20	13, 46	78.4% <.0001

The reference columns (left) show the effect size estimates for the overall meta-analysis (All studies) and the reference levels of the independent variables for the meta-regression models. For the continuous independent variables (AEX volume and baseline score), the reference condition is the weighted mean level of the independent variable across studies. The comparison columns show the effect size estimates for the comparison level of the dichotomous independent variable and show the unit size for the continuous independent variables. The

comparison – reference columns show the associations between the independent variables and the effect sizes. For dichotomous independent variables, this is the effect size estimate for the difference between the comparison and reference levels of the independent variable. For continuous independent variables, this is the effect size estimate for every unit increase in the independent variable. The far right column of p values represents the significance of the Cochran's Q heterogeneity tests.

SD, standard deviation; CI, confidence interval; I^2 , % of total variation among studies attributable to between-study heterogeneity; GXT, graded exercise test

* 8 studies (236 participants) had data for both comfortable and fastest walking speed. Comfortable and fast walking speed were pooled together because walking speed type was not a significant predictor of walking speed changes and there were no statistically significant interactions between walking speed type and any of the independent variables (all p 0.55).

Table 3

AEX Volume Breakdown Sensitivity Analysis

Reference		Comparison condition		Comparison - Reference		Between Study Heterogeneity	
Subgroup/condition	Model Estimate	95% CI		Model Estimate	95% CI	SD Model Estimate	SD 95% CI
VO_{2-peak} mL/kg/min (N=15 studies; n=598 participants)							
Mean AEX volume (26 h)	2.2	1.3, 3.1	Every 10 h unit ↑	0.4	-0.2, 0.9	1.3	0.8, 3.1
Mean AEX session duration (41 min)	2.2	1.2, 3.1	Every 10 min unit ↑	0.2	-0.7, 1.1	1.4	0.9, 3.1
Mean AEX frequency (2.9 sessions/week)	2.1	1.1, 3.0	Every 1 session/week unit ↑	0.7	-0.7, 2.1	1.3	0.8, 3.1
Mean total AEX duration (12 weeks)	2.2	1.2, 3.1	Every 4 week unit ↑	0.2	-0.3, 0.7	1.3	0.8, 3.1
Walking Speed, m/s (N=13 studies; n=415 participants*)							
Mean AEX volume (24 h)	0.06	0.01, 0.11	Every 10 h unit ↑	0.00	-0.04, 0.04	0.08	0.05, 0.19
Mean AEX session duration (41 min)	0.06	0.01, 0.11	Every 10 min unit ↑	-0.02	-0.06, 0.03	0.07	0.05, 0.19
Mean AEX frequency (3.3 sessions/week)	0.06	0.01, 0.11	Every 1 session/week unit ↑	0.07	-0.01, 0.15	0.06	0.04, 0.18
Mean total AEX duration (11 weeks)	0.06	0.01, 0.11	Every 4 week unit ↑	-0.00	-0.03, 0.03	0.08	0.05, 0.19
6-Minute Walk Test Distance, m (N=16 studies; n=734 participants)							
Mean AEX volume (29 h)	28	14, 42	Every 10 h unit ↑	-4	-12, 5	19	12, 49
Mean AEX session duration (40 min)	28	16, 39	Every 10 min unit ↑	-16	-29, -3	15	9, 37
Mean AEX frequency (4.8 sessions/week)	26	-1, 52	Every 1 session/week unit ↑	-2	-19, 14	20	13, 51
Mean total AEX duration (12 weeks)	29	15, 43	Every 4 week unit ↑	-1	-8, 7	21	13, 49

This sensitivity analysis tested different ways of decomposing AEX volume for each meta-regression.

Table 4

Summary of Data Extraction Sensitivity Analysis

Reference		Comparison			Comparison - Reference		Between Study Heterogeneity	
Subgroup/condition	Model Estimate	95% CI	Subgroup/condition	Model Estimate	95% CI	Model Estimate	SD	95% CI
VO_{2-peak}, mL/kg/min (N=15 studies; n=598 participants)								
All studies	2.2	1.3, 3.1	-	-	-	-	1.3	0.8, 3.0
Moderate AEX intensity	1.7	0.8, 2.5	Vigorous intensity	3.8	2.3, 5.2	2.1	0.9	0.5, 3.5
Mean baseline VO _{2-peak} (14.6 mL/kg/min)	2.2	1.5, 2.9	Every 1 mL/kg/min unit ↑	-	-	0.4	0.9	0.5, 2.9
Walking Speed, m/s (N=13 studies; n=415 participants)								
All studies	0.06	0.01, 0.11	-	-	-	-	0.08	0.06, 0.17
Seated AEX mode	-0.05	-0.16, 0.05	Walking mode	0.08	0.04, 0.13	0.13	0.06	0.03, 0.16
6-Minute Walk Test Distance, m (N=16 studies; n=734 participants)								
All studies	29	15, 43	-	-	-	-	20	13, 48
Seated AEX mode	4	-13, 21	Walking mode	39	26, 51	35	11	5, 155

This sensitivity analysis used different p values and different within subject repeated measures correlations (0.50 to 0.99) for variance calculations that were uncertain due to limited reporting of needed data. For each row, the model with the result closest to the null hypothesis is reported.

Table 5

Summary of Bayesian Sensitivity Analysis

Reference		Comparison			Comparison - Reference		Between Study Heterogeneity		
Subgroup/condition	Model Estimate	95% CrI	Subgroup/condition	Model Estimate	95% CrI	Model Estimate	SD Model Estimate	SD 95% CrI	DIC
VO_{2-peak}, mL/kg/min (N=15 studies; n=598 participants)									
All studies	2.2	1.3, 3.1	-	-	-	-	1.3	0.6, 2.3	55.9
Moderate AEX intensity	1.5	0.9, 2.3	Vigorous intensity	3.8	2.6, 5.1	2.3	0.5	0.0, 1.6	56.4
Mean baseline VO _{2-peak} (14.6 mL/kg/min)	2.2	1.5, 2.8	Every 1 mL/kg/min unit ↑	-	-	0.4	0.7	0.1, 1.6	54.0
Walking Speed, m/s (N=13 studies; n=415 participants)									
All studies	0.06	0.01, 0.11	-	-	-	-	0.07	0.03, 0.14	-66.9
Seated AEX mode	-0.05	-0.15, 0.05	Walking mode	0.09	0.04, 0.14	0.14	0.06	0.03, 0.11	-69.2
6-Minute Walk Test Distance, m (N=16 studies; n=734 participants)									
All studies	27	14, 40	-	-	-	-	19	10, 34	150.5
Seated AEX mode	5	-4, 15	Walking mode	38	28, 47	32	1	0, 17	148.2

The model estimate for the between study SD is the median of its posterior distribution. All other estimates are means of posterior distributions.

SD, standard deviation; CrI, credible interval; DIC, deviance information criterion, an estimate of expected predictive error (lower indicates better model fit)