High Intensity Exercise for Walking Competency in Individuals with Stroke: A Systematic Review and Meta-Analysis

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Objective: To assess the effects of high intensity exercise on walking competency in individuals with stroke. *Data sources:* A systematic electronic searching of the PubMed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (EBSCOhost), and SPORTSDiscus (EBSCOhost) was initially performed up to June 25, 2019. *Study selection:* Randomized controlled trials or clinical controlled trials comparing any walking or gait parameters of the high intensity exercise to lower intensity exercise or usual physical activities were included. The risk of bias of included studies was assessed by the Cochrane risk of bias tool. The quality of evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system. *Data extraction:* Data were extracted by 2 independent coders. The mean and standard deviation of the baseline and endpoint scores after training for walking distance, comfortable gait speed, gait analysis (cadence, stride length, and the gait symmetry), cost of walking, Berg Balance Scale , Time Up&Go (TUG) Test and adverse events were extracted. *Data Synthesis:* A total of 22 (n = 952) studies were included. Standardized mean difference (SMD), weighted mean difference (WMD), and odds ratios (ORs) were used to compute effect size and subgroup analysis was conducted to test the consistency of results with different characteristics of exercise and time since stroke. Sensitivity analysis was used to assess the robustness of the results, which revealed significant differences on walking distance (SMD = .32, 95% CI, .17-.46, $P < .01$, $I^2 = 39\%$; WMD = 21.76 m), comfortable gait speed (SMD = .28, 95% CI, .06-.49, $P = .01$, $I^2 = 47\%$; WMD = .04 m/s), stride length (SMD = .51, 95% CI, .13-.88, $P < .01$, $I^2 = 0\%$; WMD = .12 m) and TUG (SMD = −.36, 95% CI, −.72 to .01, $P = .05$, $I^2 = 9\%$; WMD = −1.89 s) in favor of high intensity exercise versus control group. No significant differences were found between the high intensity exercise and control group in adverse events, including falls (OR = 1.40, 95% CI, .69-2.85, $P = .35$, $I^2 = 11\%$), pain (OR = 3.34, 95% CI, .82-13.51, $P = .09$, $I^2 = 0\%$), and skin injuries (OR = 1.08, 95% CI, .30-3.90, $P = .90$, $I^2 = 0\%$). *Conclusions:* This systematic review suggests that high intensity exercise could be safe and more potent stimulus in enhancing walking competency in stroke survivors, with a capacity to improve walking distance, comfortable gait speed, stride length, and TUG compared with low to moderate intensity exercise or usual physical activities.

Key Words: Exercise therapy—intensity—Stroke—gait—meta-analysis

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Stroke, the second highest cause of death after ischemic heart disease, is a strong cause of activity limitations and difficulties in walking.[1,2] According to the Copenhagen stroke study,[2] 22% of survivors are unable to walk, 14% walk with a aid and less than 10% get enough walking speed and endurance, to restore the independence and normal community participation.[3] The gait energy cost of stroke patients are 1.5 to 2 times than their nondisabled peers.[4] Impaired cardiorespiratory fitness after stroke may also contribute to further walking limitations, especially in relation to endurance.[5] Achieving and maintaining the ability to walk independently in the home or community is not only closely related to independence in activities of daily living, but also an important aim of stroke rehabilitation.[6] Moreover, standing balance capacity is an important risk factor for fall and a strong predictor of walking competency and functional recovery after stroke.[7]

Physical activity has been proved to be beneficial for muscle oxidative capacity, muscle endurance, and walking function in people with multiple sclerosis[8] and stroke.[9] Meta-analysis showed that aerobic exercise contributed to improving aerobic capacity and walking performance.[10] However, most traditional stroke rehabilitation programs lack essential training time and sufficient exercise intensity.[11] The inpatient stroke survivors spent 76% of the daytime hours (8:00 a.m.-5:00 p.m.) in bed or sitting, and only 23% of the time in standing or walking.[12] The gait improvements observed were correlated with the progression of treadmill velocity.[13] Higher intensity training showed more improvement in walking distance and gait speed.[14] As far as authors know, there is no systematic review examining the effect of high intensity exercise on walking competency in comparison to low to moderate intensity exercise. Therefore, the objective of the present study was to evaluate the evidence and safety of high intensity interventions related to improving walking functional outcomes after stroke. Furthermore, we explored the most effective intensity, duration, type of intensive training, and time since stroke for stroke subjects by a consecutive subgroup analysis.

Methods

The review and analysis was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement guidelines.[15] The systematic review protocol was registered in PROSPERO (CRD42019136763).

Definitions

We defined stroke as stroke as rapidly developing clinical symptoms and/or signs of focal, or of cerebral function lasting more than 24 hours or leading to death, with no apparent nonvascular cause according to the definition of the World Health Organization. There are 3 phase after stroke: the hyper acute or acute phase (0-7days), the early subacute phase (7 days until 3 months), the late subacute phase (3-6 months), and the chronic phase (>6 months).[16]

Exercise therapy was defined as a plan of physical activities intended to strengthen muscles and the cardiovascular system (Medical Subject Heading; MeSH). Intensity of exercise refers to the rate of work, effort or metabolic needs of aerobic exercise, which can be quantified in a variety of ways, such as HR, rating of perceived exertion (RPE), rate of oxygen consumption (VO_2), watts, and walking speed/incline.[17] High intensity in stroke rehabilitation is generally defined as 60%-84% HRR/VO_2peak, 70%-89% HR max, or 14-16 Borg RPE (6-20 scale).[11]

Walking competency refers to the ability that walking proficiently and safely in the home or community, including "walking at adequate speeds to cross the street safely, walking the distances necessary to accomplish basic and instrumental activities of daily living, independently negotiating kerbs, turning the head while walking and maintaining balance, maintaining stability despite unexpected perturbations, and demonstrating anticipatory strategies to avoid or accommodate upcoming obstacles".[18] Outcomes examined included walking distance measured using 6MWT, comfortable gait speed, as an important measure of the individual's normal ambulation ability in the community, over a short distance (eg, 10MWT) instead of fast gait speed was assessed,[19] gait analysis (cadence, stride length, and the symmetry ratio), cost of walking (Cw), and balance capacity. Berg Balance Scale (BBS) was considered as the most commonly used assessment tool throughout stroke rehabilitation, and an effective, appropriate measure of balance impairment in patients with stroke. Time Up&Go (TUG) Test is a simple test used to assess both static and dynamic aspects of balance.[20]

Search Strategy

PubMed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (EBSCOhost), and SPORTSDiscus (EBSCOhost) were searched from the earliest available date to June 25, 2019. Search terms are listed in Supplemental Table I. Reference lists of retrieved articles and relevant reviews were also searched and assessed additional eligible publications.

Inclusion and Exclusion Criteria

The article was subsequently read and thoroughly assessed for following inclusion or exclusion criteria: (1) Study design: all randomized controlled trials or clinical controlled trials; (2) Patients: individuals (≥18 years of age) at acute, subacute, or chronic stages of stroke recovery; (3) Intervention: A detailed description of the high intensity exercise intervention, including intensity, duration, and frequency; The mode of training using electric devices, such as treadmills, cycle ergometer, and recumbent stepper are included in our review, but not those using auxiliary devices, such as walkers, splints, or functional electrical stimulation. Studies would be excluded if training was applied in combination with another interventions (eg, psychotherapy, physical factors therapy, gait training, and multisensory training); (4) Control: low to moderate intensity exercise (<60% HRR/VO_2peak, <70% HRmax, or <14 RPE), usual physical activities or no any exercise interventions; (5) Outcomes: 6MWT, gait analysis (cadence, stride length and the gait symmetry), Cw, BBS, TUG, comfortable gait speed (only speeds identified as comfortable, habitual, or self-selected were included; fast gait speed was excluded). The secondary outcome measures included adverse events (eg, falls, pain, and injuries). And the study statistic could be transformed into an effect size (eg, means/standard deviation [SD], 95% CI and/or *P* values); (6) The included studies were further limited to be published in English. Conference abstract, case reports, observational studies, and studies without available data were excluded.

Risk of Bias

Methodological quality of the each RCT was independently assessed by two authors according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations which suggest using the Cochrane risk of bias tool. The first part of the tool assesses 7 specific domains, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other issues. The second part assigns a judgment relating to the risk of bias for each domain which includes "low risk" of bias, "high risk" of bias or, "unclear risk" of bias. Decisions were compared and discussed to achieve consensus. A third reviewer was consulted if disagreement persisted.

Quality of Evidence

The quality of evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system. The GRADE approach specifies 4 levels of quality: high, moderate, low, or very low. The highest quality rating is for randomized trial evidence. Review authors can, however, downgrade randomized trial evidence to moderate, low, or even very low quality evidence, depending on the presence of the 5 factors, including limitations in the design and implementation, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results and high probability of publication bias.[21]

Data Extraction

A data extraction sheet based on the Cochrane Handbook for Systematic Reviews. Data were extracted from the published reports of all the eligible studies. Data from the included articles were extracted based on the Cochrane Handbook for Systematic Reviews using a standardized Excel (Microsoft Inc) data extraction form by the primary reviewer (Shiqiang Zhu) and checked by the secondary reviewer (Luoyi Shi). Disagreements were resolved by discussion and consensus. The data extraction form includes:

1. Study characteristics: study year published, country and design;
2. Participant characteristics: participant numbers, mean age, time since stroke;
3. Interventions: type, dose (frequency, intensity, and duration) according to the American College of Sports Medicine, type of control group (low to moderate intensity training, care-as-usual, no activity, or other control);
4. Outcomes: 6MWT, comfortable gait speed, stride length, cadence, gait symmetry and Cw, BBS, TUG, adverse events.

If one study provided multiple follow-up endpoints (eg, follow-up after 3, 6, and 9 months), we chose the first endpoint after completion of the intervention. If the median and range were reported, as well as the interquartile range, we converted them to the mean and SD. And if the primary outcomes (means ± SDs) were not available, we used the changes from baseline (also called a change score), if provided within the study. When the same data were observed in multiple publications, the first published study was chosen for the analysis. We tried to contact the corresponding author to get the missing information.

Statistical Analysis

Stata V.14.0 (Stata Statistical Software: Version 14.0) and Revman V.5.3.4 (Review Manager: version 5.3.4) were used to conduct the meta-analysis. Data were pooled for each intervention for which at least 2 included studies with comparable outcomes were identified. We chose standardized mean difference (SMD) with 95% CI as summary statistics used for meta-analysis. And the weighted mean difference (WMD) of various outcomes from pre- to postintervention between groups in each study (the study that only provided the changes from baseline was removed) was also calculated. The Mantel-Haenszel method was used to calculate pooled ORs for the adverse events. We used the I-squared test to assess the statistical heterogeneity of the treatment effect among studies, I^2 values of 25%, 50%, and 75% were identified as low, moderate, and high heterogeneity, respectively. Fixed effect models were applied if statistical heterogeneity was low. Otherwise, random effect models were utilized.

Four analyses with subgroups were planned: time since stroke (subacute <6 months versus chronic ≥6 months), intensity (<70% HRR/VO_2peak versus ≥70% HRR/

VO_2peak), mode (ie, treadmill, cycle ergometer, and recumbent stepper) and duration (<12 weeks versus ≥12 weeks) of intervention in experimental group. To assess the robustness of our results, sensitivity analysis was subsequently performed by computing the effects using fixed effects model or random effects model. Contour-enhanced funnel plot of each trial's effect size against the standard error was used to assess the publication bias based upon reporting of the main outcomes (included studies ≥10). We assessed funnel plot asymmetry using Begg and Egger tests with *P* value less than.1 defined as significant publication bias. The trim-and-fill computation was used to estimate the effect of publication bias on the interpretation of the results. Based on the classification of Cohen, effect sizes were defined as small (.2-.5), medium (.5-.8), or large (≥.8).[22]

Results

Studies Retrieved

Figure 1 showed the study selection process. Twenty-two studies were included in the meta-analysis. About 4418 articles retrieved through initial database searching. After titles, abstracts, full texts, and reference lists screened according to inclusion and exclusion criteria, 22 studies finally included in quantitative synthesis. Table 1 summarizes the descriptive characteristics of the 22 studies that met inclusion criteria for the review.

Characteristics of Included Studies

There were 21 RCTs and 1 controlled trial involving 952 participants (male = 600 [63%], female = 352 [37%]). The mean ages of participants ranged from 45 (8.2) to 71.3 (7.0) years, with the majority having a mean age in the 60's. The mean time since stroke ranged from 4.9 (5.8) days to 5.2 (2.93) years, with the following distribution: within 6 months (n = 7) and greater than 6 months (n = 15). Most of high intensity interventions included treadmill (n = 13) and cycle ergometer (n = 8). The intensity of exercise (range 60%-85% HRR/VO_2peak) and total time (range 25-50 minutes, with most training lasting 30 to 40 minutes [n = 18]) as well as weekly frequency (range 2-5 times, with most training 3 times per week [n = 11]) and duration (range 4-24 weeks, with 11 studies being between 8 and 12 weeks in length) varied widely between studies. Control group performed 28−45 minutes aerobic exercise (ie, underground walking, stretching exercise, usual physical therapy) at planned intensities below 50% HRR/VO_2peak.There are 17 studies reporting walking distance measured by 6MWT, 11 studies reporting comfortable gait speed measured by 10MWT, 7 studies reporting BBS, 5 studies reporting Cw, 4 studies reporting stride length, gait symmetry, cadence, and TUG. There are 6 studies reporting adverse events in detail, including non-injurious falls; pain in joint, back, muscle or chest; and skin injuries (ie, cuts, bruises, and scrapes). We used the changes from baseline instead of final values based upon guidelines from the Cochrane Handbook for Systematic Reviews of Interventions in 3 studies investigating 6MWT and 1 study investigating 10MWT for the no available data from post-treatment (means ± SDs)[24,41] and considerable differences in the baseline.[33]

Risk of Bias

Risk of bias for efficacy analysis for each included RCT is shown in Figure 2. Tang et al[42] were assessed to be at high risk of bias in random sequence generation due to the prospective matched control design. There are 13 studies in which randomization was performed by a person with no other role on the study and also 13 studies in which outcome measures were performed by blinded assessors. All studies reported whole expected outcome.

Main Analysis

The pooled analysis demonstrated significant effect size without statistically significant between-study heterogeneity on walking distance (n = 777, SMD = .32 [Fixed], 95% CI, .17-.46, $P < .01$, $I^2 = 39\%$; n = 708, WMD = 21.76 m; Fig 3), comfortable gait speed (n = 345, SMD = .28[Fixed], 95% CI, .06-.49, $P = .01$, $I^2 = 47\%$; n = 329, WMD = .04 m/s; Fig 4A), stride length (n = 117, SMD = .51[Fixed], 95% CI, .13-.88, $P < .01$, $I^2 = 0\%$; n = 117, WMD = .12 m; Fig 5A) and TUG (n = 120, SMD = −.36[Fixed], 95% CI, −.72 to .01, $P = .05$, $I^2 = 9\%$; n = 120, WMD = −1.89 seconds; Fig 6B) in favor of high intensity exercise versus control group. However, the pooled analysis showed no significant effect size on Cw (n = 146, SMD = −.07[Fixed], 95% CI, −.40 to .27, $P = .70$, $I^2 = 20\%$; n = 130, WMD = 0 mL/kg/m; Fig 4B), cadence (n = 117, SMD = .27[Random], 95% CI, −.32 to .85, $P = .38$, $I^2 = 57\%$; n = 117, WMD = 6.29 step/min; Fig 5B), gait symmetry (n = 128, SMD = .74 [Random], 95% CI, −.04 to 1.52, $P = .06$, $I^2 = 76\%$; n = 128, WMD = .08; Fig 5C), and BBS (n = 363, SMD = .10[Fixed], 95% CI, −.10 to .31, $P = .33$, $I^2 = 0\%$; n = 363, WMD = .19; Fig 6A). The pooled analysis failed to showed significant differences between the high intensity exercise and control group in falls (n = 210, OR = 1.40[Fixed],95% CI, .69-2.85, $P = .35$, $I^2 = 11\%$; Fig 7A), pain (n = 100, OR = 3.34 [Fixed], 95% CI, .82-13.51, $P = .09$, $I^2 = 0\%$; Fig 7B), and skin injuries (n = 56, OR = 1.08[Fixed], 95% CI, .30-3.90, $P = .90$, $I^2 = 0\%$; Fig 7C). Visual interpretation of funnel plots suggested no obvious evidence of publication bias on walking distance ($P = .74$) and comfortable gait speed ($P = .13$).

Quality of Evidence

The quality of evidence was moderate for the outcome of walking distance and comfortable for the lack of allocation concealment or blinding in most included studies.

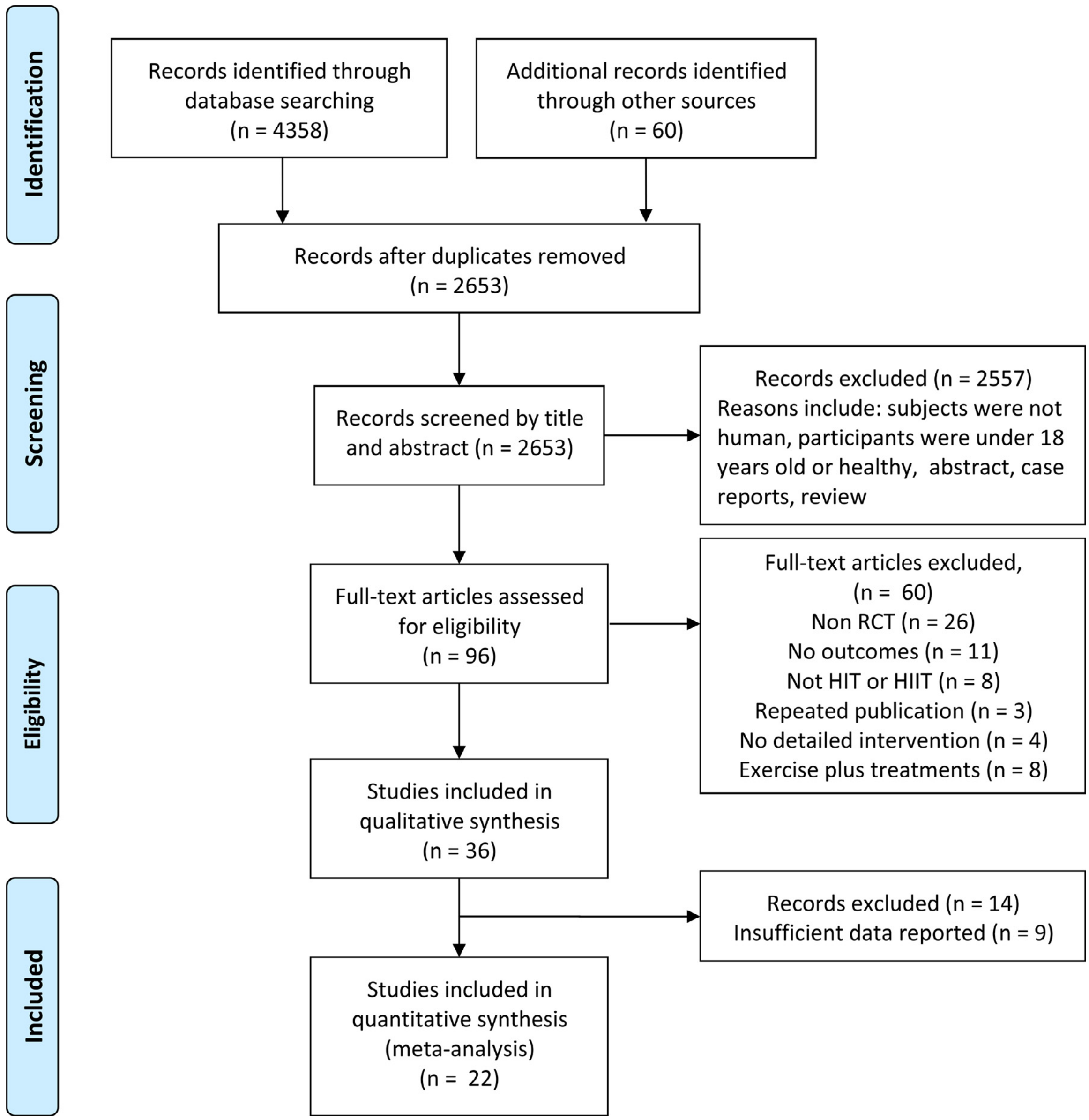

Figure 1. *PRISMA flowchart diagram of the search process.*

The quality of evidence was also rated as moderate for the outcome of stride length and TUG for the imprecision. The quality of evidence was downgraded to low for the outcome of Cw and BBS, owing to the risk of bias and imprecision, and downgraded to low for the outcome of cadence, owing to the inconsistency and imprecision. The summary and finding of the quality of evidence was showed in Table 2.

Subgroup Analysis

Subgroup analysis, conducted just on walking distance, comfortable gait speed, Cw, and BBS but else outcomes for the insufficient data, showed that higher intensity exercise (≥70% HRR/VO_2peak) revealed significant effect size on walking distance(7 studies, n = 218, SMD = .46, $P = .02$, $I^2 = 18\%$; 6 studies, WMD = 50.85 m; Supplemental Fig 1) and comfortable gait speed(5 studies, n = 127, SMD = .40, $P = .03$, $I^2 = 43\%$; 4 studies, WMD = .01 m/s; Supplemental Fig 5), instead of the intensity less than 70% HRR/VO_2peak(walking distance: 6 studies, n = 327, SMD = .21, $P = .06$, $I^2 = 64\%$; 5 studies, WMD = 8.14 m; comfortable gait speed:3 studies, n = 130, SMD = −.06, $P = .72$, $I^2 = 0\%$; 3 studies, WMD = −.01 m/s). High intensity interventions that just were performed within 6 months after stroke got the significant improvement in comfortable gait speed (4 studies, n = 150, SMD = .53, $P < .01$, $I^2 = 0\%$; 4 studies, WMD = .17 m/s; Supplemental Fig 8), instead of chronic phase during stroke recovery (7 studies, n = 195, SMD = .09, $P = .55$, $I^2 = 54\%$; 6 studies, WMD = .01 m/s). Moreover, subgroup analysis showed that high intensity

Table 1. *Characteristics of the studies included in this review*

Author, year, country	Sample size, study design	Time since stroke	Mean age (y)	Control	Mode	Intervention			Frequency	Outcomes
						Intervals		Total time (min)		
						High	Recovery			
Bang et al[23] 2016, Korea	nE = 6, nC = 6, RCT	13.7 mo	E: 56.8 C: 63.7	30 min self-selective intensity exercise	Cycle ergometer	50%-80% HRmax		30	5 days a week/4 weeks	6MWT, Comfortable 10MWT
Boyne et al[24] 2016, America	nE = 11, nC = 5, RCT	3.8 y	E: 59 C: 57	25 min at 45%-50% HRR	Treadmill	30 s at maximum safe speed	30-60s rest	25	3 days a week/4 weeks	6MWT, Comfortable 10MWT, Cw
Globas et al[13] 2012, Switzerland	nE = 18, nC = 18, RCT	60.2 mo	E: 68.6 C: 68.7	Conventional care physiotherapy	Treadmill	60%-80% HRmax		30-50	3 days a week/18 weeks	6MWT, Comfortable10MWT, BBS
Gordon et al[25] 2013, Jamaica	nE = 64, nC = 64, RCT	11.8 mo	E: 64.9 C: 63.4	Massage to the affected side	Treadmill	60%-				85%HRmax
	30	3 days a week/12 weeks	6MWT							
Holleran et al[26] 2015, America	nE = 6, nC = 6, RCO	35 mo	E: 55 C: 55	30%-40% HRR	Treadmill	70%-80% HRR		30	4 weeks	6MWT, Comfortable 10MWT, Cw
Hornby et al[27] 2016, America	nE = 15, nC = 17, RCT	89 d	E: 57 C: 60	30%-40% HRR	Treadmill	70%-80% HRR		40	4-5 days a week/10 weeks	6MWT, Comfortable 10MWT, gait symmetry, BBS, TUG
Ivey et al[28] 2015, America	nE = 18, nC = 15, RCT	75.3 mo	E: 61 C: 63	50% HRR	Treadmill	80%-85% HRR		30	24 weeks	6MWT, Comfortable 10MWT,
Jin et al[29] 2012, China	nE = 68, nC = 65, RCT	17.9 mo	E: 57 C: 56	20%-30% HRR	Cycle ergometer	6-10min 50%-70% HRR	2-3 min rest	40	5 days a week/8 weeks	6MWT, BBS
Lamberti et al[30] 2017, Italy	nE = 17, nC = 18, RCT	34 mo	E: 67 C: 69	Low-intensity overground walking	Treadmill	60%-70% HRR		30	3 days a week/8 weeks	6MWT, BBS, TUG
Lau et al[31] 2011, China	nE = 13, nC = 13, RCT	16.5 d	E: 72.5 C: 74.5	Conventional gait therapy	Treadmill	1-2 min maximum safe speed	A recovery period	30	3 days a week/4 weeks	stride length, cadence, BBS
Leddy et al[32] 2016, America	nE = 21, nC = 12, RCT	89 d	E: 55 C: 61	30%-40% HRR	Treadmill	70%-80% HRR		40	10 weeks	Comfortable 10MWT, Cw

Table 1 (*Continued*)

Author, year, country	Sample size, study design	Time since stroke	Mean age (y)	Control	Mode	Intervention			Frequency	Outcomes
						Intervals		Total time (min)		
						High	Recovery			
Lee et al[33] 2008, Australia	nE = 12, nC = 12, RCT	52.4 mo	E: 67.2 C: 65.3	Sham cycling	Cycle ergometer	50%-70% VO_2peak		30	10-12 weeks	6MWT, Comfortable 10MWT, Cw
Macko et al[34] 2005, America	nE = 32, nC = 29, RCT	35 mo	E: 63 C: 64	30%-40% HRR	Treadmill	60%-70% HRR		40	3 days a week/18 weeks	6MWT,Comfortable 10MWT, Cw
Mahtani et al[35] 2016, America	nE = 23, nC = 13, RCT	106 d	E: 54 C: 61	30%-40% HRR	Treadmill	70%-80% HRR		40	4-5 days a week/10 weeks	stride length, cadence, gait symmetry
Munari et al[36] 2016, Italy	nE = 8, nC = 7, RCT	5.2 y	E: 61 C: 62	55 min at 80% self-selected speed	Treadmill	5 × 5-min at 85%-95% VO_2peak	3 min at 50% VO_2peak	40	3 days a week/12 weeks	6MWT, stride length, cadence, gait symmetry, TUG
Pang et al[37] 2005, Canada	nE = 32, nC = 31, RCT	5.1 y	E: 65.8 C: 64.7	Seated upper extremity program	Cycle ergometer	70%-80% HRR		30	3 days a week/19 weeks	6MWT, BBS
Pohl et al[38] 2002, Germany	nE = 20, nC = 20, RCT	16.2 wk	E:58.2 C: 61.6	Conventional gait therapy	Treadmill	1-2 min maximum safe speed	A recovery period	30	3 days a week/4 weeks	Comfortable 10MWT, stride length, cadence
Quaney et al[39] 2009, America	nE = 19, nC = 19, RCT	> 6 mo	E: 64.1 C: 58.9	Stretching exercise	Cycle ergometer	70% HRmax		45	3 days a week/8 weeks	BBS, TUG
Sandberg et al[40] 2016, Sweden	nE = 29, nC = 27, RCT	4.9 d	E: 71.3 C: 70.4	Standard care	Cycle ergometer	50%-80% HRmax		30	2 days a week/12 weeks	6MWT
Severinsen et al[41] 2014, Denmark	nE = 16, nC = 13, RCT	14 mo	E: 69 C: 66	<60% 1RM	Cycle ergometer	60%-70% HRR		45	12 weeks	6MWT
Tang et al[42] 2009, Canada	nE = 23, nC = 22, CCT	17.8 d	E: 64.7 C: 65.7	Usual individualized treatment	Cycle ergometer	50%-75% WRpeak		30	3 days a week/4-5weeks	6MWT, Comfortable 10MWT, gait symmetry
Tang et al[43] 2014, Canada	nE = 22, nC = 25, RCT	4.0 y	E: 65.9 C: 66.9	<40% HRR	Cycle ergometer	70%-80% HRR		30-40	24 weeks	6MWT

BBS, Berg Balance Scale; C, control; CCT, clinical controlled trial; Cw, cost of walking; E, experimental; HRmax, maximum heart rate; HRR, heart rate reserve; RCO, randomized cross-over; RCT, randomized controlled trial; TUG, Time Up&Go Test; VO_2peak, peak oxygen consumption; WRpeak, peak work rate; 6MWT, 6-minute walk test; 10MWT, 10-metre walk test.

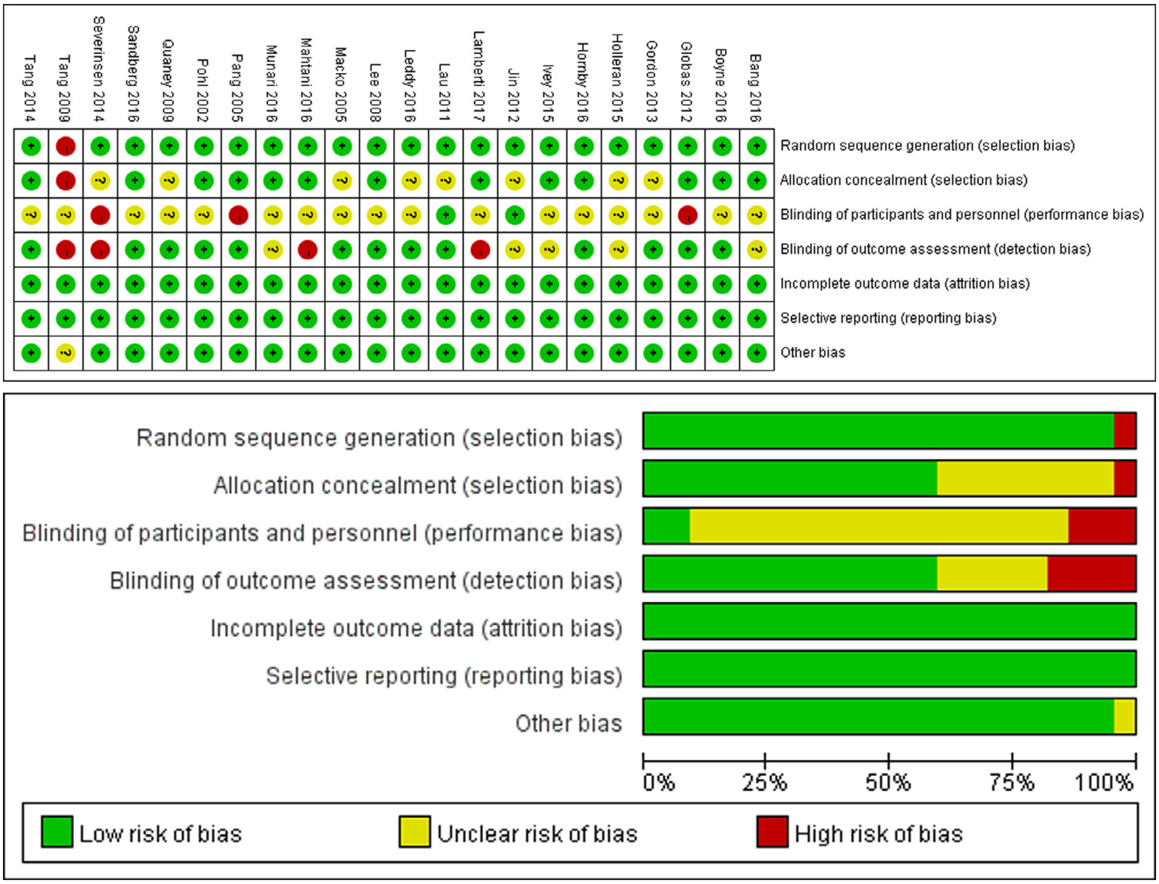

Figure 2. *Risk of bias of included studies in this review.*

treadmill training (8 studies, n = 264, SMD = .28, $P = .03$, $I^2 = 55\%$; 7 studies, WMD = .04 m/s; Supplemental Fig 6) for less than 12 weeks (8 studies, n = 214, SMD = .52, $P < .01$, $I^2 = 33\%$; 7 studies, WMD = .09 m/s; Supplemental Fig 7) reported significant effect size in comfortable gait speed, rather than exercise using cycle ergometer (3 studies, n = 81, SMD = .27, $P = .24$, $I^2 = 39\%$; 3 studies, WMD = .05 m/s) lasting more than 12 weeks (3 studies, n = 131, SMD = −.08, $P = .65$, $I^2 = 0\%$; 3 studies, WMD = −.01 m/s). Despite of no significant differences observed, subgroup analysis revealed better effect size of higher intensity exercise (≥70% HRR/VO_2peak) on Cw (Supplemental Fig 9) and BBS (Supplemental Fig 10).

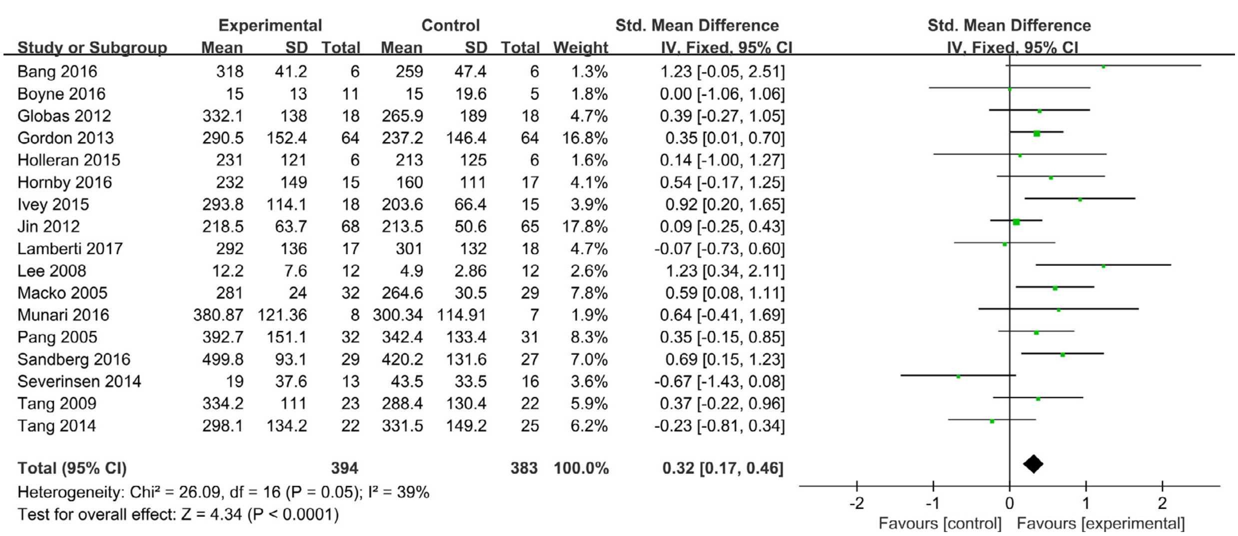

Figure 3. *Summary effect sizes postintervention for walking distance.*

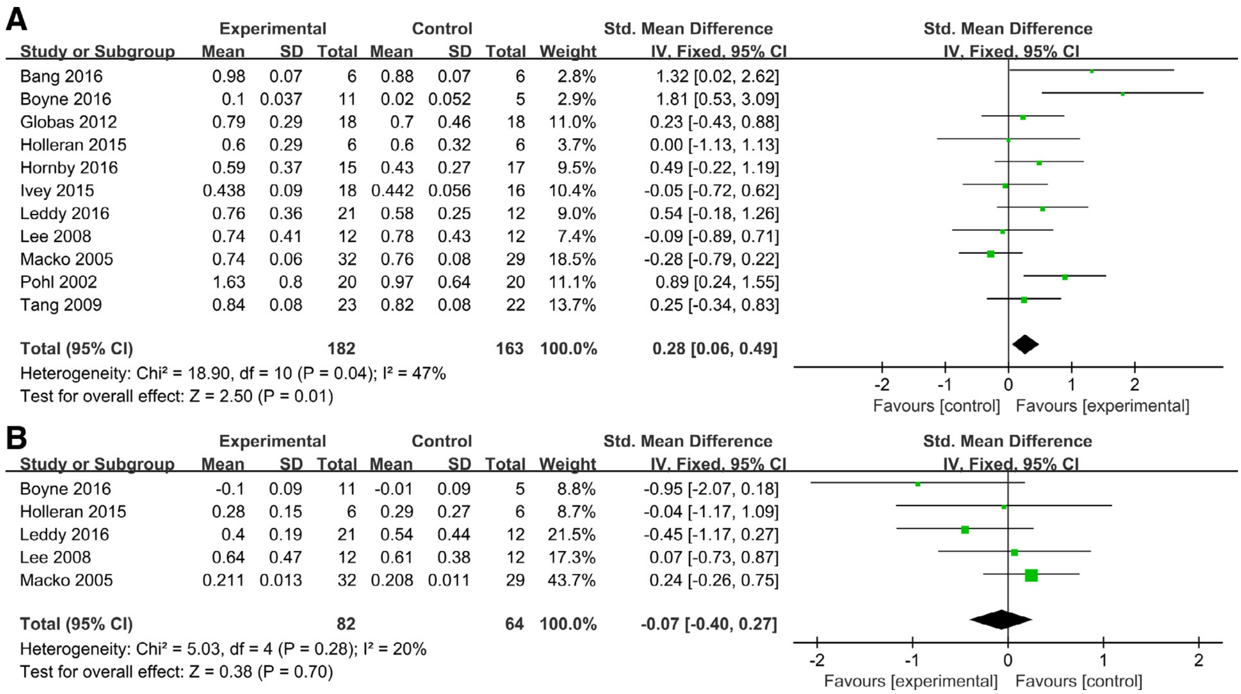

Figure 4. *(**A**) Summary effect sizes postintervention for comfortable gait speed. (**B**) Summary effect sizes postintervention for Cw.*

Sensitivity Analysis

The sensitivity analysis showed that results except gait symmetry and TUG were robust when random or fixed effects model was applied in analysis (Table 3).

Discussion

The present meta-analysis included 22 trials that investigated the effects of high intensity exercise dedicated to walking competency and gait-related functions in stroke

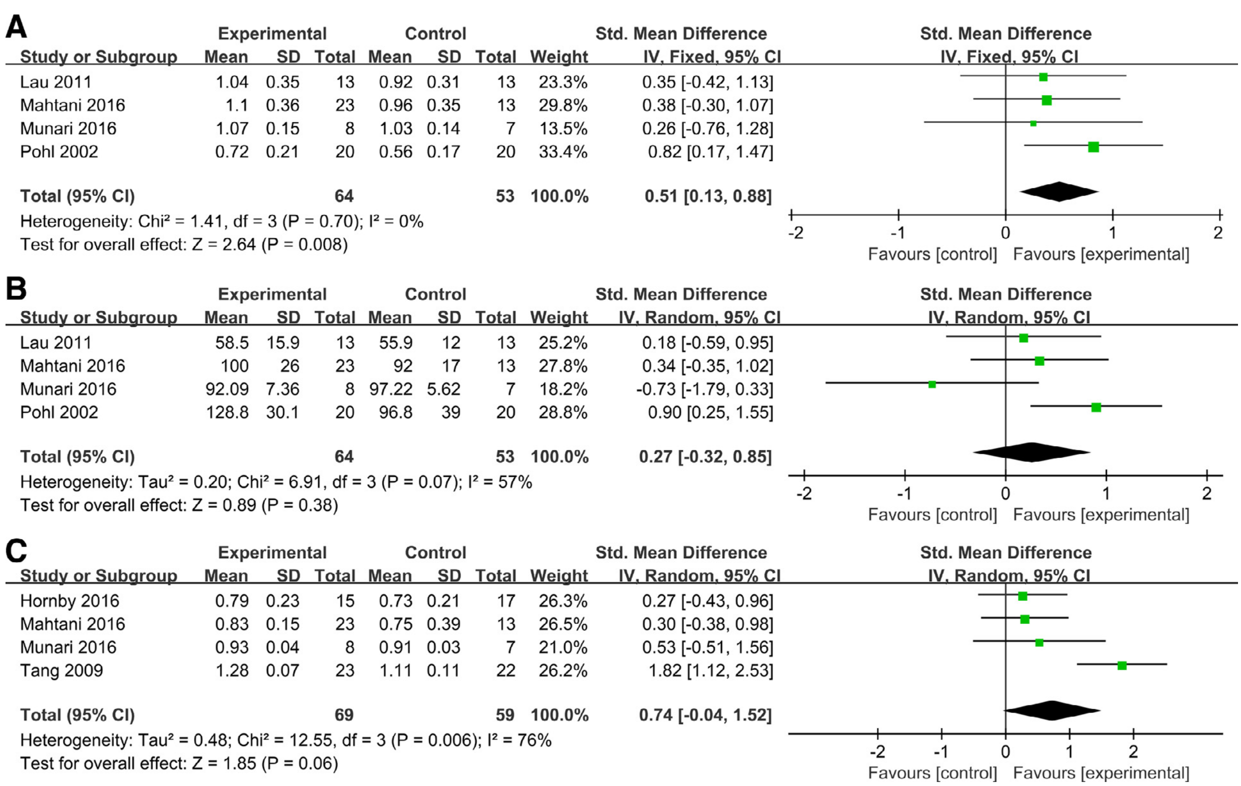

Figure 5. *(**A**) Summary effect sizes postintervention for stride length. (**B**) Summary effect sizes postintervention for cadence. (**C**) Summary effect sizes postintervention for gait symmetry.*

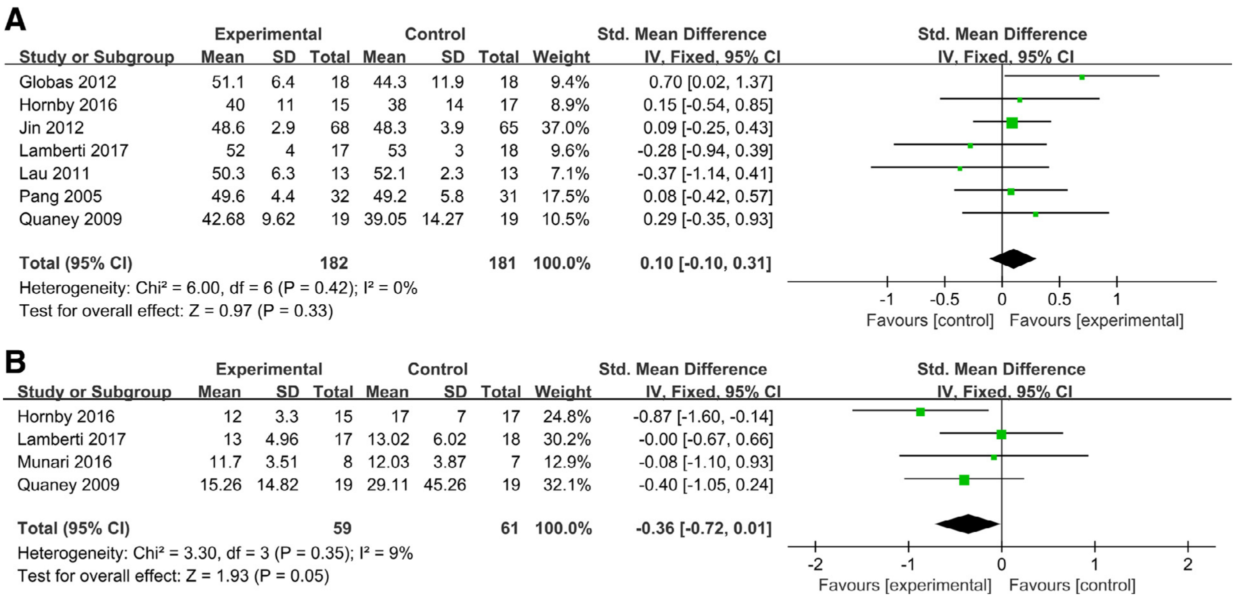

Figure 6. *(**A**) Summary effect sizes postintervention for BBS. (**B**) Summary effect sizes postintervention for cost of TUG.*

survivors. Based on the results from the pooled analysis, it is shown that patients with stroke benefit from high intensity exercise with regard to walking distance, comfortable walking speed, stride length, and TUG.

Walking performances are important for stroke patients to maintain their own lives and participate in family, social activities. Various high-intensity training protocols have also been shown to improve community mobility,[44] peak

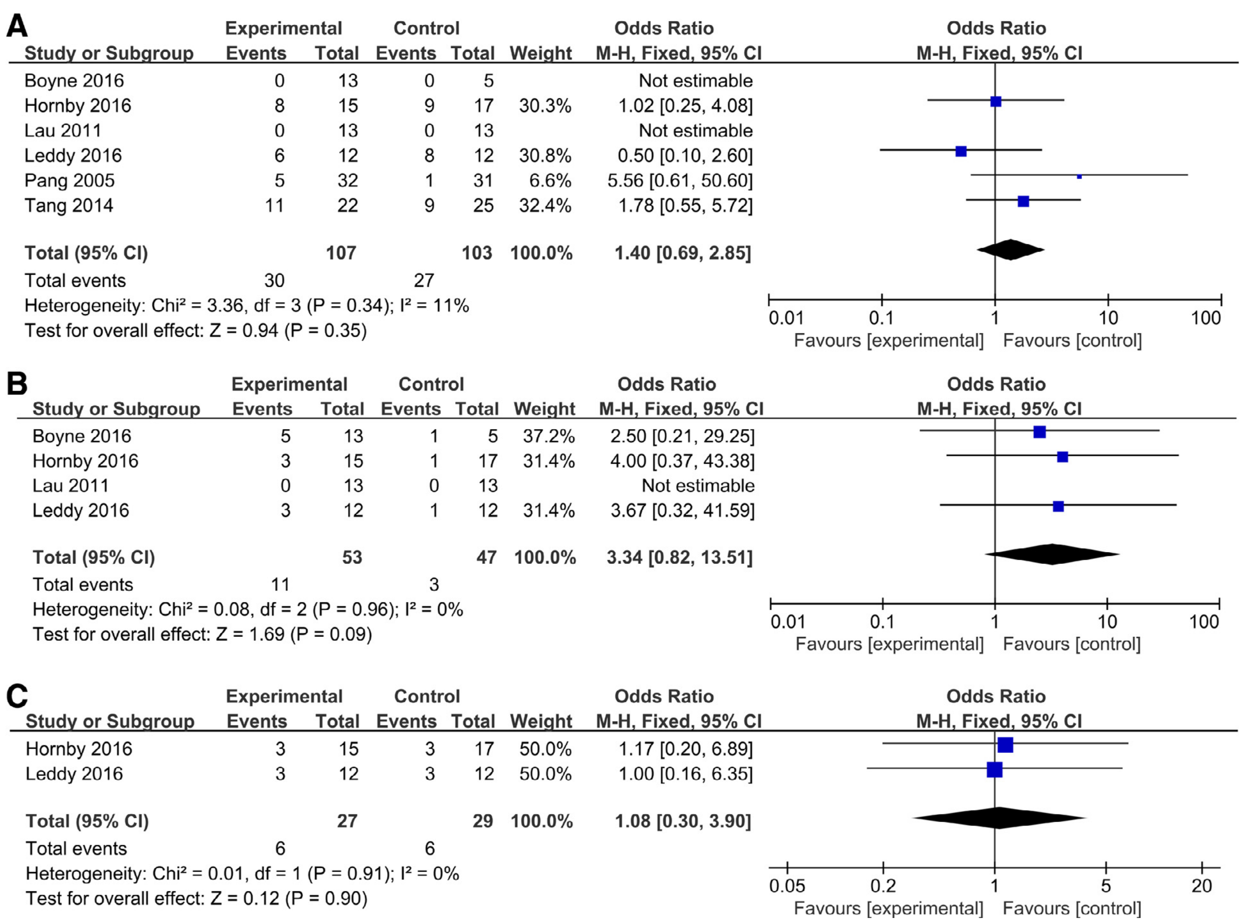

Figure 7. *(**A**) Summary effect sizes postintervention for adverse events of falls. (**B**) Summary effect sizes postintervention for adverse events of pain. (**C**) Summary effect sizes postintervention for adverse events of injuries.*

Table 2. *GRADE summary of findings of quality of evidence*

Patient or population: patients with stroke
Intervention: GRADE

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Grade				
Walking distance		The mean walking distance in the intervention groups was .32 standard deviations higher (.17 to .46 higher)		777 (17 studies)	⊕⊕⊕⊝ Moderate[†]	SMD .32 (.17-.46)
Comfortable gait speed		The mean comfortable gait speed in the intervention groups was .28 standard deviations higher (.06-.49 higher)		345 (11 studies)	⊕⊕⊕⊝ Moderate[†]	SMD .28 (.06-.49)
Cw		The mean cw in the intervention groups was .07 standard deviations lower (.4 lower-.27 higher)		146 (5 studies)	⊕⊕⊝⊝ Low[†]	SMD −.07 (−.4 to .27)
Stride length		The mean stride length in the intervention groups was .51 standard deviations higher (.13-.88 higher)		117 (4 studies)	⊕⊕⊕⊝ Moderate[†]	SMD .51 (.13-.88)
Cadence		The mean cadence in the intervention groups was .27 standard deviations higher (.32 lower to .85 higher)		117 (4 studies)	⊕⊕⊝⊝ Low[†]	SMD .27 (−.32 to .85)
Gait Symmetry		The mean gait symmetry in the intervention groups was .74 standard deviations higher (.04 lower to 1.52 higher)		128 (4 studies)	⊕⊕⊝⊝ Low[†]	SMD .74 (−.04 to 1.52)
BBS		The mean bbs in the intervention groups was .1 standard deviations higher (.1 lower to .31 higher)		363 (7 studies)	⊕⊕⊝⊝ Low[†]	SMD .1 (−.1 to .31)

(*Continued*)

Table 2 (*Continued*)

Patient or population: patients with stroke Intervention: GRADE						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Grade				
TUG		The mean tug in the intervention groups was .36 standard deviations lower (.72 lower to .01 higher)		120 (4 studies)	⊕⊕⊕⊝ Moderate†	SMD −.36 (−.72 to .01)
Falls	Study population		OR 1.4 (.69-2.85)	210 (6 studies)	⊕⊕⊝⊝ Low†	
	262 per 1000	332 per 1000 (197-503)				
	Moderate					
	196 per 1000	254 per 1000 (144-410)				
Pain	Study population		OR 3.34 (.82-13.51)	100 (4 studies)	⊕⊕⊕⊝ Moderate†	
	64 per 1000	185 per 1000 (53-479)				
	Moderate					
	71 per 1000	203 per 1000 (59-508)				
Injuries	Study population		OR 1.08 (.3-3.9)	56 (2 studies)	⊕⊕⊝⊝ Low†	
	207 per 1000	220 per 1000 (73-504)				
	Moderate					
	213 per 1000	226 per 1000 (75-514)				

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
Abbreviations: CI: Confidence interval; OR: Odds ratio.
*The basis for the *assumed risk* (eg, the median control group risk across studies) is provided in footnotes. The *corresponding risk* (and its 95% confidence interval) is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its 95% CI).
†No explanation was provided.

Table 3. *Sensitivity analysis*

Outcome	Analysis	RCTs(n)	SMD	95%CI	*P* value	I^2
Walking distance	**Model**					
	Random	17	.34	[.14, .54]	.00	39%
	Fixed	17	.32	[.17, .46]	.00	39%
Comfortable gait speed	**Model**					
	Random	11	.34	[.03, .65]	.03	47%
	Fixed	11	.28	[.06, .49]	.01	47%
Cw	**Model**					
	Random	5	−.10	[−.50, .29]	.60	20%
	Fixed	5	−.07	[−.40, .27]	.70	20%
Gait symmetry	**Model**					
	Random	4	.74	[−.04, 1.52]	.06	76%
	Fixed	4	.75	[.37, 1.12]	**.00***	76%
Stride length	**Model**					
	Random	4	.51	[.13, .88]	.00	0%
	Fixed	4	.51	[.13, .88]	.00	0%
Cadence	**Model**					
	Random	4	.27	[−.32, .85]	.38	57%
	Fixed	4	.35	[−.03, .73]	.07	57%
TUG	**Model**					
	Random	4	−.36	[−.74, .03]	.07	9%
	Fixed	4	−.36	[−.72, .01]	**.05***	9%
BBS	**Model**					
	Random	7	.10	[−.10, .31]	.33	0%
	Fixed	7	.10	[−.10, .31]	.33	0%

*Results were not robust when random or fixed effects model was applied.

aerobic capacity[13] or gait economy,[44] and quality of life.[27] The baseline levels of 6MWT in all but 4 studies were below 300 m. Although the 6 minutes walking distance in the pooled analysis improved 21.76 m, the mean improvement of 50.85 m in higher intensity exercise (≥70% HRR/VO_2peak) showed in subgroup analysis was 42 m more than the exercise programs with high intensity less than 70% HRR/VO_2peak and was about twice time than the minimal clinically important difference for the 6MWT during cardiac rehabilitation program in coronary artery disease patients (25 m[45]). Moreover, subgroup analysis showed high intensity treadmill training preformed lasting more than 12 weeks in patients within 6 months poststroke elicited slightly better effect on walking distance. Previous literature has shown that an average walking speed of 1.1-1.5 m/s might be enough for pedestrian to walk proficiently and safely in different domestic and social environments.[46] There was small but significant effect size in comfortable gait speed after high intensity training, corresponds to a mean improvement of .04m/s, which still lower than minimal clinically important difference for the 10MWT (.3 m/s[45]). But the trend toward greater improvement among the experimental group is noteworthy. The mean comfortable walking speed (.81 m) after high intensity exercise reached the level of full community ambulation (>.8 m/s), whereas the control group (.70 m/s) was within the range of limited community walking (.4-.8 m/s).[47, 48] Similarly, the pooled analysis of 4 high quality studies showed medium effect size in the stride length after high intensity exercise, corresponds to a mean improvement of .12 m and reaching to the mean level of .98 m, which was longer than the mean stride length of the community-dwelling elderly (.88 m).[49] Balance and mobility are the most important functional limitations in patients with chronic stroke.[50] The TUG test is a single-task measure and BBS is the multiple-task measure for assessing balance and mobility in patients with stroke. The present review showed significant improvement in TUG but not in BBS after high intensity exercise. A previous systematic review reported that the multiple-task measure was better than a single-task measure in evaluating balance.[51] However, the use of BBS not only often take a long time and could not detect specific balance deficits,[52] but also has a ceiling effect during the chronic phase poststroke. Indeed, 5 out of 7 studies reported near-normal BBS scores (>48 points) in the experimental group after high intensity exercise. The relatively modest gains on the BBS might have led to an underestimation of high intensity therapy effects in the patients with stroke. Although the subgroup analysis revealed no significant differences between intensity and time of exercise for the BBS, higher intensity training (≥70% HRR/VO_2peak) for more than 12 weeks showed better effect size. Therefore, we recommend to use the scales (eg, dynamic gait index, mini-BES Test) in the future with high test-retest reliability, construct validity, and lower ceiling effect for evaluating the therapy effects for balance in high-functioning stroke survivors.[53,54] The present review failed to report significant differences in cadence, gait symmetry, and Cw, which were proved to be correlated with the progression of treadmill velocity[13] and inclination.[36] A stepwise treadmill inclination resulted in reduced cadence, a longer stride length, and a prolonged stance and a reduced relative swing phase of the hemiplegic side lower limb with improved symmetry of swing duration.[55] Moreover, the motion mode of lower limbs have adaptive change by long-term training on sloping treadmill which could improve gait symmetry, increase stride length and frequency, reduce the tension of hamstring tendon.[36] Murri et al[36] assessed the Cw at the 50%, 60%, 80%, and 100% of the self-selected speed and results showed that Cw in this specific population attains its minimal 100% self-selected speed. In the high intensity treadmill training group, however, significant result within-group comparisons was obtained only at 100% of self-selected speed after training. Cw is speed dependent: the relationship between Cw and velocity is usually described by a "U-shaped curve" in which the "U-shaped curve" reaches a minimum of 100% self-selection speed.[36] The present review failed to report significant differences between high intensity exercise and control group in terms of falls, pain and skin injuries. Thus, poststroke high intensity exercise might be safe for further studies with appropriate screening, monitoring, and precautions.

Study Limitations

There were several limitations. First, few trials included in the review provided clear descriptions of the blinding of participants and most failed to perform an intention-to-treat analysis, which could be sources of bias. Second, the statistical power of the present meta-analysis might be moderate in some outcomes (eg, cadence, gait symmetry, TUG, and Cw) due to the low number of studies included, particularly in the subgroup analysis, which may have resulted in a type II error (eg, false-negative outcome). Third, our restricting this review to papers only published in English could also lead to bias affecting the outcome of this meta-analysis. Fourth, various definitions of "intensity" as well as complex rehabilitation interventions in experimental and control groups likely affected the objectivity and reliability of this meta-analysis. Fifth, 3 of the 22 studies reported changes from baseline and required some conversion of the data, which might partially increase the heterogeneity and error. Finally, most studies recruited individuals in the chronic phase poststroke with mild or moderate deficits and without unstable or serious cardiovascular conditions. Therefore, the effects of high intensity exercise in other subpopulations (eg, individuals with severe impairments, higher cardiac risks) needs further investigations.

Conclusions

This systematic review and meta-analysis suggests that high intensity exercise could be safe and more potent stimulus in enhancing walking competency in stroke survivors, with a capacity to improve walking distance, comfortable gait speed, stride length, and TUG compared with low to moderate intensity exercise or usual physical activities. Besides, this review and subgroup analysis also proved a high intensity exercise program (70%-85% HRR/VO_2peak, 3-5 times lasting 30-40 minutes per week for 8-12 weeks) which is beneficial for walking competency in patients with subacute and chronic stroke. Large high-quality randomized controlled trials in the future are still warranted to determine an optimal protocol of high intensity exercise applied in the individual at different stage of stroke recovery.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.104414.

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