What Is the Dose-Response Relationship Between Exercise and Cardiorespiratory Fitness After Stroke? A Systematic Review

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Background. Exercise after stroke improves cardiorespiratory fitness and walking capacity; however, the effect of altering exercise dose (via frequency, intensity, time, and type) on fitness or walking capacity is unclear.

Purpose. The purpose of this study was to synthesize the current evidence for the effects of different doses of exercise on cardiorespiratory fitness and walking capacity in people after stroke.

Data Sources. Seven relevant electronic databases were searched using keywords relating to stroke and cardiorespiratory fitness.

Study Selection. Trials that compared more than 1 dose of exercise for people (≥ 18 years old) after stroke and measured peak oxygen consumption or 6-minute walk test distance as an outcome were included. Two reviewers independently appraised all trials.

Data Extraction. Two reviewers independently extracted data from included articles. Intervention variables were extracted in accordance with the Template for Intervention Description and Replication checklist.

Data Synthesis. Data were synthesized narratively. Nine trials involving 279 participants were included. Three of 5 trials comparing exercise intensity showed that higher-intensity training was associated with greater improvements in cardiorespiratory fitness. The effects of other exercise dose components (frequency, time, and type) on fitness were not determined. Overall, walking capacity improved as program length increased.

Limitations. All trials had a high risk of bias, and most had a high rate of attrition. Most trials included people more than 6 months after stroke and who walked independently, limiting the generalizability of the findings.

Conclusions. Exercising at an intensity greater than 70% of heart rate reserve can be more effective in increasing cardiorespiratory fitness after stroke than exercising at lower intensities. More trials that compare exercise doses by manipulating only 1 dose parameter at a time for people after stroke are needed.

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[Galloway M, Marsden DL, Callister R, Erickson KI, Nilsson M, English C. What is the dose-response relationship between exercise and cardiorespiratory fitness after stroke? a systematic review. *Phys Ther.* 2019;99:821–832.]

Published Ahead of Print: March 05, 2019
Accepted: September 30, 2018
Submitted: February 9, 2018

Low cardiorespiratory fitness is associated with an increased risk of stroke, cardiovascular disease, and all-cause mortality.[1–3] Low levels of cardiorespiratory fitness are common in people after stroke compared with people who are healthy and matched for age and sex.[4] Many types of exercise interventions are effective in increasing poststroke cardiorespiratory fitness[5,6] and reducing secondary stroke risk factors such as raised systolic blood pressure, increased plasma concentations of cholesterol, fasting glucose, and insulin .[7] However, the optimal or most effective dose for exercise prescription is not clear.[5,6] Current guidelines for clinical management poststroke[8–10] recommend doses ranging from 20 to 40 minutes of moderate-to-vigorous–intensity exercise on most days of the week, though the evidence supporting these doses for people after stroke is limited.

Determining the dose-response to exercise training after stroke is difficult for a number of reasons. First, the 4 main parameters used to quantify exercise dose—frequency, intensity, time (session duration and program length), and type (FITT[11])—are not always comprehensively or accurately reported in trials.[12,13] Second, even when prescribed doses are reported it is often difficult to verify that the doses were delivered.[6] Finally, the majority of trials in stroke have measured the effect of a single dose of exercise, and few have directly compared 2 or more doses.[5,6] Of trials comparing more than 1 dose, some have manipulated more than 1 dose parameter at a time, have not adequately controlled other dose parameters, or have done both.[14] The manipulation of 1 dose parameter while controlling all other FITT parameters has been used in trials of populations who are healthy and provides the original understanding of the FITT parameters of fitness dose.[15,16]

Most reviews have found significant improvements in cardiorespiratory fitness in response to exercise for people with stroke, but have been unable to determine the relationship between cardiorespiratory fitness and exercise dose. [4–6] This is likely due to the meta-analyses in these reviews being limited by high heterogeneity of dose parameters, participant characteristics, or both. One review found greater improvements in cardiorespiratory fitness with higher doses of exercise intensity.[14] However, the exercise doses compared across studies did not always hold all other FITT components constant. To our knowledge, no previous reviews have limited their inclusion criteria to studies in which 2 or more doses of exercise were directly compared.

The primary aim of this systematic review was to determine the effect of different doses of exercise on cardiorespiratory fitness in people after stroke. We hypothesized that a higher dose of exercise would be associated with greater improvements in cardiorespiratory fitness. Second, we also aimed to quantify the dose-response of FITT parameters on cardiorespiratory fitness. Finally, because tests of walking capacity (such as the 6-minute walk test) are clinically important measures of people's ability to walk further, longer, or faster,[17] we also aimed to determine the effect of different doses of exercise on walking capacity.

Methods

The conduct and reporting of this review (Prospero Registration: 40068) were guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[18]

Data Sources and Searches

A systematic search was undertaken of MEDLINE, CINAHL, EMBASE, PsycINFO, AMED, SPORTDiscus, and Cochrane Library databases from their inception to June 2016. Keywords relating to stroke and cardiorespiratory fitness were used and the strategy adjusted to suit each database. The search strategy used for MEDLINE is shown in Table 1. We also hand searched articles identified in the reference lists of included articles and relevant systematic reviews. The final search was conducted on May 10, 2018.

Inclusion criteria were as follows:

Design: any study design, published in peer-reviewed English language journals.
Participants: adults who were ≥ 18 years old and had had a stroke.
Interventions: more than 1 dose of aerobic exercise was delivered and the stated aim of the trial was to improve cardiorespiratory fitness or the intervention was deemed capable of improving cardiorespiratory fitness (eg, by including target heart rates or training intensities or by progressively increasing the intervention intensity or volume).
Exercise doses differed in at least 1 of the following parameters: frequency, intensity, time (session duration and program length), and exercise type.
Outcome measures: at least 1 of the following outcomes was reported: peak oxygen consumption ($\dot{V}O_{2peak}$) (mL/kg/min or L/min) measured during either a graded exercise test or a 6-minute walk test; distance walked (m) during a 6-minute walk test.

Trials were excluded if they:

were published in thesis or abstract form only;
evaluated 1 dose of exercise training against no intervention or against any other intervention that was not conventional fitness training.

Study Selection

Two independent reviewers (M.G. and D.L.M.) screened the titles and abstracts and categorized trials for eligibility based on inclusion and exclusion criteria. Full-text articles were read by both reviewers and reasons for exclusion

Table 1.
Search Strategy Used for MEDLINE[a]

Search	Term(s)
1	Stroke/
2	Cerebrovascular Disorders/
3	Brain Injuries/and stroke.mp.
4	Hemiplegia/
5	Oxygen Consumption/
6	VO2*.mp.
7	(cardio* and fit*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8	Exercise Test/
9	6MWT.mp.
10	6* min* walk*.mp.
11	six* min* walk*.mp.
12	1 or 2 or 3 or 4
13	5 or 6 or 7 or 8 or 9 or 10 or 11
14	12 and 13

[a]Terms were adapted for other databases. 6MWT = 6-minute walk test; VO2 = peak oxygen consumption.

were documented. Disagreements were resolved through discussion between the 2 reviewers, and if necessary, adjudicated by a third reviewer (C.E.).

Data Extraction

Authors M.G and D.L.M. independently extracted data from included articles. Extracted data were then cross-checked and any discrepancies resolved through discussion between the 2 reviewers, and if necessary adjudicated by a third reviewer (C.E.). Intervention variables were extracted in accordance with the Template for Intervention Description and Replication checklist.[19,20]

Quality Assessment

Quality and risk of bias of trials were assessed by 2 independent reviewers (M.G. and C.E.) using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (chapter 8).[21] This assessment method rates the risk of bias in studies across the following domains: selection, performance, detection, attrition, reporting, and any other identified biases. If ratings differed, a third assessor (D.M.) adjudicated. We searched for published protocols for all included trials to determine whether outcome reporting bias was present.

Data Synthesis and Analysis

Data were synthesized narratively. Total exercise time (minutes) was calculated by multiplying frequency (sessions per week) by session duration (minutes) by program length (weeks). Trials were examined closely for clinical heterogeneity; in particular, similarities and differences in clinical populations, intervention types, and doses were noted.

Role of the Funding Source

The study was supported by a Stroke Foundation of Australia Small Project Grant (2016). C.E. was supported by a National Heart Foundation Future Leaders Fellowship (2017–2020). M.G. was supported by an Australian Postgraduate Scholarship (2016–19) and a Barker PhD Scholarship (2017–2018). The funders had no role in the design and execution of the study, in the analyses and interpretation of the data, or in the decision to submit results.

Results

Study Identification

The Figure outlines the flow of articles, including reasons for exclusion. Of 2185 citations identified, 118 full-text articles were screened, and 9 trials (279 participants) that met our criteria were included.[22–30]

Characteristics of Included Trials

Trial characteristics, including details of interventions used, are described in the supplementary material (available at https://academic.oup.com/ptj). All trials were published between 2001 and 2016; 1 was conducted in Denmark,[23] 7 were conducted in the United States,[22,25–30] and 1 trial was conducted in both Germany and the United States.[24] Four trials were conducted by members of the same research group.[24,25,27,28] Study designs included: 4 randomized controlled trials,[27–30] 3 single group trials

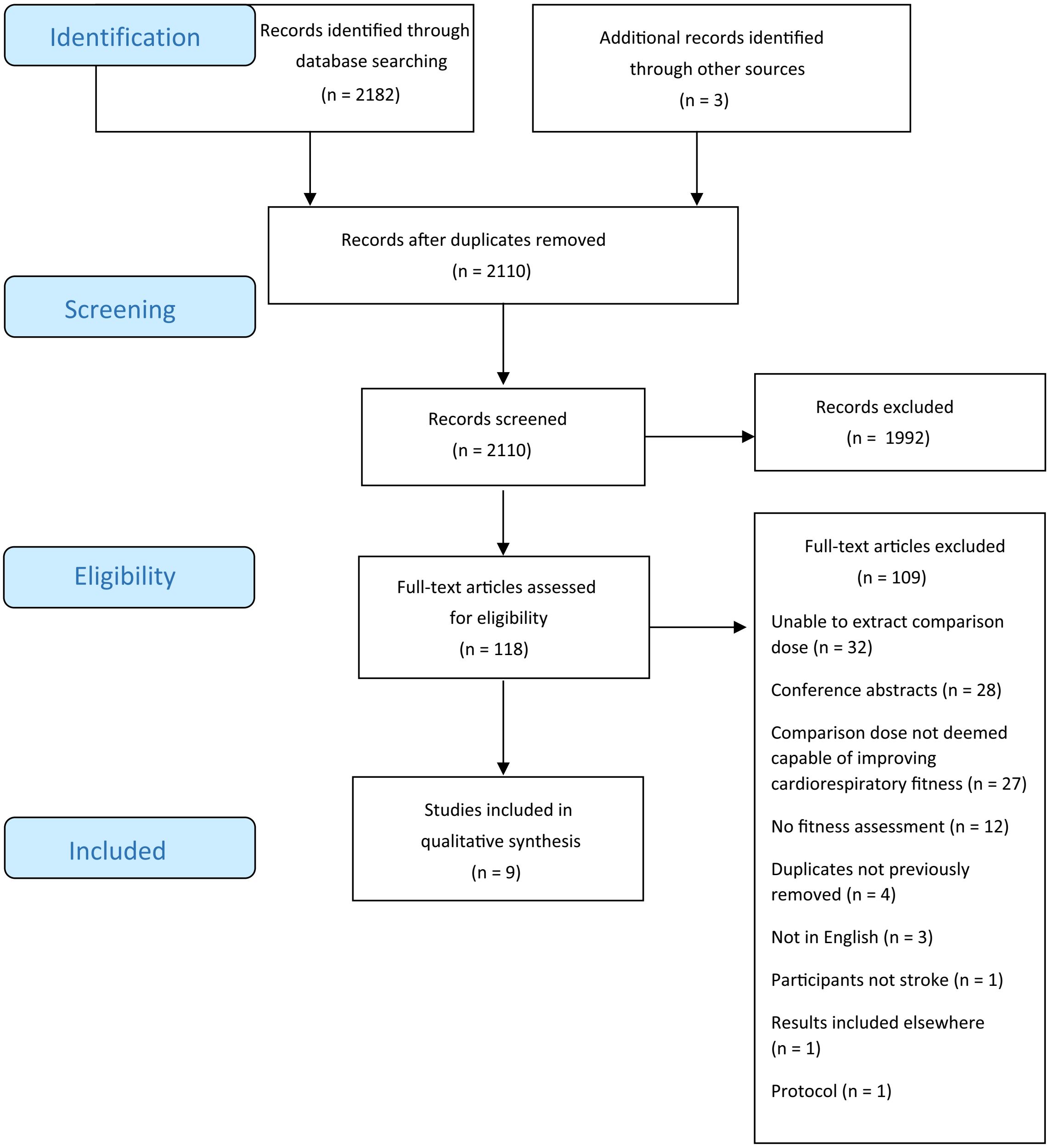

Figure.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

with repeated measures,[22,23,25] and 1 nonrandomized trial.[26] One study was a post hoc analysis of 2 randomized controlled trials.[24]

Risk of Bias

The risk of bias of the included trials is summarized in Table 2. Eight of 9 trials had a high risk of bias for 3 or more categories, and 6 (67%) had high risk of bias for 4 or more categories. Only 4 (44%) included random allocation to group, only 1 used allocation concealment, and only 2 (22%) used assessors who were masked with regard to group allocation. The risk of bias for selective reporting was unclear for 6 (67%) of the trials.

Participant Characteristics

Participant characteristics are summarized in Table 3. The 9 trials reported results on 279 participants (n = 167; 60% male). All participants were able to walk independently,

Table 2.
Risk of Bias of Included Trials

Trial	Random Sequence Generation	Allocation Concealment	Masking of Participants and Personnel	Masking of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias
Boyne et al[30] (2016)	Low	Low	High	Low	Low	Low	High
Holleran et al[22] (2014)	High	High	High	High	High	Unclear	Low
Holleran et al[29] (2015)	Low	High	High	High	High	Unclear	Low
Ivey et al[27] (2015)	Low	High	High	High	High	Low	Low
Jorgensen et al[23] (2010)	High	High	High	High	High	Unclear	Low
Lam et al[24] (2010)	High	High	High	Low	High	High	High
Luft et al[28] (2008)	Low	High	High	Low	High	Unclear	Low
Macko et al[25] (2001)	High	High	High	High	High	Unclear	Low
Rimmer et al[26] (2009)	High	High	Low	High	Low	Unclear	Low

with inclusion criteria ranging from mild-moderate[24,25,27,28,30] to moderate-severe[23,29] hemiplegic gait. All trials included participants who were more than 6 months poststroke. One study[22] also included a group of participants with a mean time poststroke of 3.2 months. The mean [SD] age of participants ranged from 55 [8] years[29] to 67 [8] years.[25]

Measures of Cardiorespiratory Fitness

Cardiorespiratory fitness was measured by Vo_{2peak} (mL/kg/min) in 7 trials.[24–30] Assessments were conducted using a treadmill protocol in 6 trials,[24,25,27–30] with the remaining trial measuring Vo_{2peak} during cycle ergometry.[26] No trials measured Vo_{2peak} during a 6-minute walk test. The mean [SD] baseline fitness measures of Vo_{2peak} ranged from 9.5 [3.7] mL/kg/min, reported by Holleran et al,[29] to 20.2 [1.2] mL/kg/min, reported by Lam et al.[24]

Measures of Walking Capacity

Walking capacity assessed by distance walked during the 6-minute walk test was reported in 6 trials.[22–24,27,29,30] For participants with chronic stroke, the mean [SD] distance walked at baseline during the 6-minute walk tests ranged from 167 [103] m in the study by Holleran et al [22] to 280 [28] m reported by Lam et al; for participants with subacute stroke[22] the mean was 119 [94] m.

Interventions

Details about the exercise interventions delivered in the trials are described in Table 4 and in the supplementary material (available at https://academic.oup.com/ptj). All exercise interventions occurred in clinical or laboratory settings and were supervised. All interventions included individualized progression of exercise parameters, most through either increased treadmill speed or session duration, although the detail of how this occurred was not always clear (see supplementary material; available at https://academic.oup.com/ptj). Despite strategies to improve intervention fidelity being reported in 7 trials,[22,23,26–30] dropout rates remained high across trials (11%–35%). Adherence to planned exercise sessions for participants who did not drop out was reported in 6 trials [22,25,27–30] and was greater than 85%.

Dose Comparisons

Details of dose comparisons regarding the frequency, intensity, time (duration and program length), and type of exercise training are shown in Table 4.

Frequency. No trials compared doses with different exercise training frequencies per week.

Intensity. Five trials compared different doses of exercise intensity.[24,26,27,29,30] Exercise intensity in these trials was reported in terms of percent heart rate reserve [%(maximum − resting heart rate) + resting heart rate],[31] with maximum (or peak) heart rate measured during baseline fitness assessments. Increases in Vo_{2peak} were greater with higher-intensity exercise in 3 trials.[24,27,30] Only 1 of these trials[30] held all other FITT components constant and found 14% greater Vo_{2peak} after higher-intensity exercise (53%–72% heart rate reserve) than after lower-intensity exercise (48%–52% heart rate reserve). In the remaining 2 trials, either program length[24] or session duration were also manipulated.[27] Vo_{2peak} was 11% greater when exercise intensity was higher (80% heart rate reserve compared with 60% heart rate reserve)

Table 3.
Characteristics of Included Trials[a]

Doses Compared by:	Trial	Trial Design	Inclusion Criteria	Group	No. of Participants	Baseline Vo_{2peak}, mL/kg/min	Baseline 6MWT Distance, m	Age, y	Sex (Men/Women)	Stroke Type (Ischemic/Hemorrhagic)	Time Since Stroke, mo
Intensity	Boyne et al[30] (2016; US)	RCT	Age = 35–90 y; ≥ 6 mo after stroke; able to walk 3 min on a treadmill at 0.13 m/s with no aerobic exercise contraindications	High-intensity interval	11	16.0 [4.0]	220 [153]	59 [9]	7/4	9/NR	45.6 [34.8]
				Moderate intensity, continuous	5	21.6 [4.0]	247 [121]	57 [12]	2/3	2/NR	75.6 [24]
	Holleran et al[29] (2015; US)	RCT (crossover design)	Age = 18–75 y; ≥ 6 mo after stroke; walking speed <0.9 m/s	High-intensity intervention first	6	11 [5.5][b]	191 [93]	55 [8.2]	7/5	NR	35 [21]
				Low-intensity intervention first	6	9.5 [3.7][b]	207 [123]				
Intensity and program length	Lam et al[24] (2010; US, Germany)	Post hoc analysis of RCTs	Age NR; ≥ 6 mo after stroke; able to walk ≥ 3 consecutive min on a treadmill at ≥ 0.1 m/s without personal or body-weight support	For US group: low intensity, longer length	20	14.1 (1.2)[c]	211 (22)[c]	64 (2.1)[c]	8/12	20/0	60.1 (20)[c]
				For Germany group: high intensity, shorter length	32	20.2 (1.2)[c]	280 (28)[c]	69 (1.1)[c]	26/6	32/0	58.3 (8.8)[c]
Intensity and session duration	Rimmer et al[26] (2009; US)	Nonrandomized controlled trial	Age > 18 y; > 6 mo after stroke; independently ambulant	Moderate intensity, shorter length	18	14.3 [6.9]	NA	56 [12.6]	6/12	NR	NR
				Low intensity, longer length	19	12.5 [3.7]	NA	59 [7.1]	8/11	NR	NR
				Control: therapeutic exercise	18	12.6 [4.2]	NA	59 [7.1]	8/10	NR	NR
	Ivey et al[27] (2015; US)	RCT	Age NR; > 6 mo after stroke; ambulant with mild-moderate hemiparetic gait	Higher intensity	18	15.9 [1.7]	238 [32]	61 [1.6]	10/8	NR	NR
				Lower intensity	16	16.6 [1.1]	172 [22]	63 [2.4]	11/5	NR	NR
Program length	Holleran et al[22] (2014; US)	Single-group repeated measures	Age = 18–75 y; subacute and chronic stroke; able to ambulate >10 m with self-selected walking speed of <0.9 m/s	Chronic group	13	NR	167 [103]	55 [8.8]	6/4	NR	42 [58]
				Subacute group	12	NR	119 [94]	52 [13]	8/4	NR	3.2 [1.8]
	Jorgensen et al[23] (2010; Denmark)	Single-group repeated measures	Age > 50 y; > 3 mo after stroke; moderate-severe gait impairment with walking speed < 50%	Single group	14	NR	210 [110]	60.4 [5.7]	13/1	NR	24.6 [23.1]
	Macko et al[25] (2001; US)	Single-group repeated measures	Age > 50 y; > 6 mo after stroke; mild-moderate hemiparetic gait	Single group	23	15.2 [2.9]	NR	67 [8]	19/4	0/23	28 [26]
	Luft et al[28] (2008; US)	RCT	Age NR; > 6 mo after stroke; able to walk ≥ 3 consecutive min on a treadmill at ≥0.09 m/s without adverse effects	T-Ex	37	12.9 [0.7]	NR	63.2 [8.7]	18/19	37/0	62.5 [13.5]
				Control	34	12.9 [0.7]	NR	63.6 [10]	20/14	34/0	44.6 [13.1]

[a] Data are means [SDs] unless otherwise indicated. 6MWT = 6-minute walk test; NA = not applicable; NR = not reported; RCT = randomized controlled trial; T-Ex = task-repetitive treadmill exercise; US = United States; Vo_2 = peak oxygen consumption.
[b] Resting Vo_2 was subtracted from measured Vo_2 before Vo_{2peak} was reported.
[c] Mean (SE).

Table 4.
Dose Comparisons and Outcomes[a]

Trial	Interventions			Outcomes			
				Change in Vo_{2peak} (mL/kg/min)		Change in 6MWT (m)	
Doses Compared by Intensity							
	Group	**High Intensity**	**Low Intensity**	**High Intensity**	**Low Intensity**	**High Intensity**	**Low Intensity**
Boyne et al[30] (2016)	F	3 times/wk	3 times/wk	2.2 (1.28)[b]	−1.3 (1.73)[b]	15 (7.14)[b]	15 (10.7)[b]
	I	**53%–72% HRR**	**48%–52% HRR**				
	T(d)	20 min[c]	20 min[c]				
	T(l)	4 wk	4 wk				
	T	Treadmill	Treadmill				
	Total	300 min	300 min				
Holleran et al[29] (2015)	F	12 sessions in 4–5 wk	12 sessions in 4–5 wk	0	1.5	40	6
	I	**70%–80% HRR**	**40%–50% HRR**				
	T(d)	40 min	40 min				
	T(l)	4–5 wk	4–5 wk				
	T	Walking	Walking				
	Total	480 min	480 min				
Doses Compared by Intensity and Program Length							
	Group	**High Intensity, Short Length**	**Low Intensity, Long Length**	**High Intensity, Short Length**	**Low Intensity, Long Length**	**High Intensity, Short Length**	**Low Intensity, Long Length**
Lam et al[24] (2010)	F	3 times/wk	3 times/wk	5.1 (0.7)[b]	2.1 (0.5)[b]	48.7 (6.8)[b]	41.3 (8.6)[b]
	I	**80% HRR**	**60% HRR**				
	T(d)	40 min	40 min				
	T(l)	**12 wk**	**24 wk**				
	T	Treadmill	Treadmill				
	Total	1440 min	2880 min				
Doses Compared by Intensity and Session Duration							
	Group	**Moderate Intensity, Short Duration**	**Low Intensity, Long Duration**	**Moderate Intensity, Short Duration**	**Low Intensity, Long Duration**		
Rimmer et al[26] (2009)	F	3 times/wk	3 times/wk	0.6	0.7		
	I	**40%–69% HRR**	**<50% HRR**				
	T(d)	**30 min**	**30–60 min**				
	T(l)	14 wk	14 wk				
	T	Treadmill	Treadmill				
	Total	1260 min	1890 min				
	Group	**High Intensity, Short Duration**	**Low Intensity, Long Duration**	**High Intensity, Short Duration**	**Low Intensity, Long Duration**	**High Intensity, Short Duration**	**Low Intensity, Long Duration**
Ivey et al[27] (2015)	F	NR	NR	5.4	1.1	56	32
	I	**80%–85% HRR**	**50% HRR**				
	T(d)	**30 min**	**50 min**				
	T(l)	24 wk	24 wk				
	T	Treadmill	Treadmill				
	Total	NA	NA				
Doses Compared by Program Length							
	Group	**Short Duration**	**Long Duration**			**Short Duration**	**Long Duration**
Holleran et al[22] (2014) (chronic)	F	≤ 40 times in 10 wk	≤40 times in 10 wk			44.5 (NR)[d]	89 (NR)

(continued)

Table 4.
Continued

Trial	Interventions			Outcomes			
				Change in Vo_{2peak} (mL/kg/min)		Change in 6MWT (m)	
	I	70%–80% HRR	70%–80% HRR				
	T(d)	60 min	60 min				
	T(l)	**5 wk**	**10 wk**				
	T	Walking, stair climbing	Walking, stair climbing				
	Total	1200 min	2400 min				
	Group	**Short Duration**	**Long Duration**			**Short Duration**	**Long Duration**
Holleran et al[22] (2014) (subacute)	F	4 times/wk	4 times/wk			72[d]	144
	I	70%–80% HRR	70%–80% HRR				
	T(d)	60 min	60 min				
	T(l)	**5 wk**	**10 wk**				
	T	Treadmill	Treadmill				
	Total	1200 min	2400 min				
	Group	**Short Duration**	**Long Duration**			**Short Duration**	**Long Duration**
Jorgensen et al[23] (2010)	F	2 times/wk	2 times/wk			120[d]	130
	I	80% HR_{max}	80% HR_{max}				
	T(d)	75 min	75 min				
	T(l)	**6 wk**	**12 wk**				
	T	Treadmill, strength	Treadmill, strength				
	Total	900 min	1800 min				
	Group	**Short Duration**	**Long Duration**	**Short Duration**	**Long Duration**		
Macko et al[25] (2001)	F	3 times/wk	3 times/wk	1.4	1.4		
	I	64% HRR	58% HRR				
	T(d)	31 min	36 min				
	T(l)	**12 wk**	**24 wk**				
	T	Treadmill	Treadmill				
	Total	1116 min	2592 min				
	Group	**Short Duration**	**Long Duration**	**Short Duration**	**Long Duration**		
Luft et al[28] (2008)	F	3 times/wk	3 times/wk	1.2	2.3		
	I	60% HRR	60% HRR				
	T(d)	40 min	40 min				
	T(l)	**12 wk**	**24 wk**				
	T	Treadmill	Treadmill				
	Total	1440 min	2880 min				

[a]Data are means [SDs] unless otherwise indicated. Dose characteristics are presented according to frequency, intensity, time (session duration and program length), and type (FITT) principles (dose comparisons for each study are shown in bold type). 6MWT = 6-minute walk test; F = frequency; HR_{max} = maximum heart rate; HRR = heart rate reserve; I = intensity; NA = not applicable; T(d) = session duration; T(l) = program length; T = type of exercise; Total = total aerobic exercise time in minutes; Vo_{2peak} = peak oxygen consumption.
[b]Mean (SE).
[c]Plus 3 min of warm-up and 2 min of cool-down.
[d]Estimated from graphs.

despite a shorter program length (3 months vs 6 months).[24] Similarly, Vo_{2peak} was also significantly greater after higher-intensity exercise (80%–85% heart rate reserve) (+ 34%) than after lower-intensity exercise (50% heart rate reserve) (+ 5%), despite a shorter session duration (30 minutes vs 50 minutes) for the higher-intensity exercise group.[27] In the remaining trials, there were no significant improvements in Vo_{2peak} after either higher- or lower-intensity exercise and no differences between groups.[26,29]

Two trials compared the effect of exercise intensity on walking capacity.[29,30] All other FITT components were kept constant. In the first trial,[29] participants walked significantly further on the 6-minute walk test after higher-intensity exercise (+ 40 m), despite not improving in measures of Vo_{2peak}. In the second trial, there was no difference in 6-minute walk test distance between higher- and lower-intensity exercise despite a greater increase in Vo_{2peak} with higher-intensity exercise.[30]

Time (session duration). No trials specifically compared doses with different exercise session durations.

Time (program length). The effect of program length on Vo_{2peak} was measured in 3 trials.[24,25,28] Two trials measured Vo_{2peak} at the middle and end of the intervention (3 and 6 months) while keeping all other FITT components constant, allowing the effect of program length to be examined.[25,28] In the trial by Luft et al,[28] participants showed greater improvements in Vo_{2peak} after 6 months of intervention compared with 3 months. In contrast, participants in the second trial showed significant improvement in Vo_{2peak} after 3 months of exercise, but no further improvements were seen between 3 and 6 months.[25] The third study was a post hoc comparison of data from 2 randomized controlled trials that used exercise interventions that varied in program length and intensity.[24] In this study, significantly greater improvements in Vo_{2peak} were seen with a 3-month program length (higher intensity) than with a 6-month program length (lower intensity).

The effect of program length on walking capacity was reported in 3 trials.[22–24] In the first trial, walking capacity was measured weekly and increased linearly up until 8 weeks, with no further improvements between 8 and 12 weeks.[23] In the second trial, walking capacity also increased linearly up to 10 weeks, but no further measures were taken after 10 weeks. [22] Finally, in the third trial there was no difference in walking capacity between a 3-month exercise program (higher intensity) and a 6-month exercise program (lower intensity).[24]

Type. No trials specifically compared exercise doses with different types or modes of exercise training.

Discussion

This review investigated the effects of different doses of exercise training on cardiorespiratory fitness in people after stroke. Nine trials that compared the effects of 2 or more doses of exercise on measures of cardiorespiratory fitness or walking capacity were identified. Improvements in fitness, although small, were clinically significant.[32] Few trials altered only 1 FITT parameter, making interpretation of the results difficult. Overall, training at higher exercise intensities was associated with greater improvements in cardiorespiratory fitness, but these results were not consistent across all trials. We were unable to quantify dose-response effects for any of the FITT parameters.

In our review, 5 trials directly compared different doses of exercise intensity, with the effect of different intensities of exercise appearing to be nonlinear. At the lower end of the intensity spectrum, 1 trial compared moderate-intensity exercise (40%–69% heart rate reserve) with low-intensity exercise (< 50% heart rate reserve) training and found no improvements in cardiorespiratory fitness with either intervention.[26] The moderate-intensity exercise arm of this trial included a gradual increase in relative intensity over a period of weeks. It is possible that once a sufficient intensity of exercise was reached, the remaining program length was insufficient to elicit improvements in cardiorespiratory fitness. However, participants showed greater improvements in cardiorespiratory fitness in trials in which exercise intensity was high (72%–85% heart rate reserve)[24,27,30] than in those with lower-intensity exercise training (< 60% heart rate reserve), even when the higher-intensity training was combined with a shorter program length[24] or a shorter session duration.[27] These data suggest that when exercise intensity is high enough, it can be more important than program length or session duration in driving fitness gains. Future studies investigating the specific effects of exercise intensity on cardiorespiratory fitness should ensure that the program length is consistent between groups, and of sufficient duration.

It was not possible to quantify the dose-response relationship between exercise intensity and fitness outcomes from this review. Only 2 studies compared the effect of intensity on cardiorespiratory fitness while holding all other parameters of dose constant.[29,30] In all other trials the effect of exercise intensity was confounded by either differences in program length[24] or session duration,[26,27] making it impossible to separate the effect of intensity alone. Furthermore, 1 study used a crossover design[29] and found that intervention order had a significant impact, suggestive of a carryover effect when the higher-intensity intervention was provided first.

Our findings regarding exercise intensity are similar to those of a previous meta-analysis,[14] which found larger effect sizes for cardiorespiratory fitness in trials involving vigorous-intensity exercise interventions after stroke compared with trials involving moderate-intensity exercise interventions. Our findings are also consistent with trials of other populations, such as older persons who are healthy,[33–35] in whom greater gains in cardiorespiratory fitness were associated with higher-intensity training. However, a more recent review of exercise training in older people who are sedentary found that if the intensity is too high (> 75%–80% heart rate reserve), then cardiorespiratory fitness can actually decline.[36] There are few studies of stroke incorporating very-high-intensity exercise,[5,6] and the safety and feasibility of this approach requires further investigation.

Three issues cloud the interpretation of the results regarding exercise intensity. First, although the intensities of prescribed doses were reported in most trials, it was not always clear what proportion of participants within these trials achieved the target exercise intensities or how consistently these were achieved. Second, most studies reported relative exercise intensity in terms of percent of heart rate reserve, which requires the input of actual or predicted maximum heart rate to calculate. Using age-predicted maximum heart rates, as occurred in some included studies,[22,23] has not been validated in stroke[37] and adds to the uncertainty in determining exercise intensity.[38] Finally, in populations such as people who have had a stroke, there is a high incidence of taking antihypertensive medications (including beta-blockers[39]). Using heart rate measures to determine relative intensity in people taking these medications might not be accurate, because the use of beta-blockers results in lower-than-expected maximum heart rates, exercise heart rates, or both.[40]

Only 3 trials[24,25,28] compared the effect of program length on cardiorespiratory fitness, and the findings were not consistent. Although cardiorespiratory fitness increased over the duration of exercise interventions included in our review, the rate of improvement varied, and sometimes plateaued. There are 2 possible reasons for this. First, other parameters of exercise dose (frequency, session duration, or exercise intensity) could have affected these findings. Where exercise intensity was maintained as program length increased, fitness gains continued.[28] When exercise intensity was inconsistent between arms of the trial[24] or decreased as program duration increased,[25] fitness gains did not continue. Maintaining or increasing the relative intensity of exercise interventions by increasing workload (eg, by increasing treadmill speeds or gradients) ensures physiological adaptations are enhanced; therefore, fitness gains are more likely to continue with longer program length. Second, most of the included trials in our review did not set out to determine the effect of different program lengths, but were single-group trials with midpoint measures.[25,28] This design is problematic in exercise trials due to the need to interrupt training schedules for assessments, and could help to explain why the number of trials that included repeated measures over the course of their interventions was low. Our findings regarding program length are similar to a previous review and meta-analysis that found programs of duration 3 months or less and more than 3 months resulted in similar gains in cardiorespiratory fitness.[6]

Regarding walking capacity, we found conflicting results. Concerning the impact of exercise intensity, the relationship between gains in fitness and walking capacity was unclear. One study reported greater improvements in walking capacity after higher-intensity training but without concurrent fitness gains.[29] By contrast, Boyne et al[30] found that although greater gains in fitness occurred with higher-intensity exercise, there was no significant effect of exercise intensity on walking capacity. These findings highlight that increases in fitness do not necessarily translate to improvements in walking capacity after stroke. Results in walking capacity tests are affected by fitness, the ability to modulate walking speed, or both—factors that are often problematic in stroke. For people with low fitness or low walking speed after stroke, the 6-minute walk test is effectively a test of maximal exercise capacity.[41] However, if it is not possible to increase walking speed due to stroke-related lower limb impairments, results on the 6-minute walk test might not reflect changes in cardiorespiratory fitness. Similarly for people with faster walking speeds at baseline (eg, > 2.0 m/s)[41] improvements in walking distance might not be possible due to a ceiling in walking speed being reached. Regarding program length, walking capacity increased with longer program length in most studies; however, this did not always match improvements in fitness. Although cardiorespiratory fitness ($\dot{V}o_{2peak}$) and 6-minute walk test distance are significantly correlated in many studies, correlations are low to moderate (0.42–0.74),[42] and Vo_{2peak} can explain only 56% to 60% of the variance in walk distance.[43,44] Improvements in gait efficiency, balance, muscle strength, or neuromotor control, which can occur simultaneously with increases in fitness, could account for some of the gains seen in 6-minute walk test distance.

Strengths and Limitations

The key strength of our review is the inclusion of trials that directly compared 2 or more different doses of exercise. This means that heterogeneity between doses was low, and our findings therefore are more robust than meta-analyses in which doses are compared between trials. However, only 9 trials (279 participants) met our inclusion criteria. Only 4 trials were randomized controlled trials, and most had a high rate of attrition. Only 1 trial used intention-to-treat analysis[30] whereas all others used "on-" or "per-protocol" analysis, which means effect size(s) can be overestimated. Most trials included people more than 6 months poststroke who were able to walk independently, limiting the generalizability of our results.

Conclusions and Clinical and Research Implications

Exercise at higher intensities (eg, > 70% heart rate reserve) can be more effective at improving cardiorespiratory fitness than exercise at lower intensities. Exercise programs should also be of sufficient length (at least 3 months) to allow time for physiological adaptations. Improvements in cardiorespiratory fitness might not always translate to improvements in walking capacity, and therefore both need to be trained specifically. There is limited current evidence of the impact of altering other dose parameters on cardiorespiratory fitness. To better understand the effect of exercise dose on cardiorespiratory fitness after stroke, we need better-designed trials that manipulate only 1 parameter of dose at a time. Without these trials, establishing the optimal dose and/or the dose-response of exercise for improving cardiorespiratory fitness is not possible, and evidence supporting exercise guidelines will remain limited.

Author Contributions

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Funding

The study was supported by a Stroke Foundation of Australia Small Project Grant (2016). C. English was supported by a National Heart Foundation Future Leaders Fellowship (2017–2020). M. Galloway was supported by an Australian Postgraduate Scholarship (2016–2019) and a Barker PhD Scholarship (2017–2018).

Systematic Review Registration

The PROSPERO registration for this study was 2016 CRD42016040068.

Disclosures and Presentations

The authors completed the ICJME Form for Disclosure of Potential Conflicts of Interest. M. Galloway and C. English reported a grant received by their institution from the Stroke Foundation—Australia. All other authors reported no conflicts of interest.
An oral presentation of this study was given at the Stroke 2018 Conference, August 7–10, 2018, Sydney, New South Wales, Australia.

DOI: 10.1093/ptj/pzz038

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