How little is enough? The feasibility of conducting a dose-escalation study for exercise training in people with stroke

Margaret Galloway,[a,e] Dianne L Marsden,[d,e,f] Robin Callister,[b,e] Kirk I Erickson,[g,h,i] Michael Nilsson,[c] and Coralie English,[a,e]

Question: Is it feasible and safe to conduct an exercise dose-finding study in people with stroke? Is it possible to determine a minimal dose of exercise required to see clinically meaningful improvements in cardiorespiratory fitness? *Methods:* Dose-escalation study. Twenty people with stroke (n=5 per cohort) who were able to walk independently participated in home-based, telehealth-supervised aerobic exercise sessions 3 d/week at moderate-vigorous intensity for 8 weeks. Dose parameters of frequency (3 d/week), intensity (55-85% of heart rate peak) and program length (8 weeks) were kept constant. The duration of exercise sessions was increased by 5 min per session from Dose 1 (10 min/session) to Dose 4 (25 min/session). Doses were escalated if safe and tolerable (< 33% of a cohort reaching a dose-limiting threshold). Doses were efficacious if ≥ 67% of a cohort increased peak oxygen consumption ≥ 2mL/kg/min. *Results:* Target exercise doses were well adhered to, and the intervention was safe (480 exercise sessions delivered; one fall resulting in minor laceration) and tolerable (no participants met the dose-limiting threshold). None of the exercise doses met our criterion for efficacy. *Conclusions:* It is possible to conduct a dose-escalation trial for people with stroke. The small cohort sizes may have limited the ability to determine an efficacious minimum dose of exercise. Providing supervised exercise session at these prescribed doses via telehealth was safe. *Registration:* The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000460303).

Keywords: Stroke—Exercise dose—Cardiorespiratory Fitness—Exercise—Telemedicine—Rehabilitation

Introduction

Low cardiorespiratory fitness is associated with an increased rate of mortality[1, 2], cardiovascular disease and stroke[3]. Cardiorespiratory fitness is up to 50% lower in stroke survivors compared with age and sex matched controls[4-6]. Improving cardiorespiratory fitness provides

From the [a]School of Health Sciences, College of Health, Medicine and Wellbeing, University of Newcastle, Newcastle, NSW, Australia; [b]School of Biomedical Sciences and Pharmacy, College of Health, Medicine and Wellbeing, University of Newcastle, Newcastle, NSW, Australia; [c]Centre for Rehab Innovations (CRI), College of Health, Medicine and Wellbeing, University of Newcastle, Newcastle, NSW, Australia; [d]College of Health, Medicine and Wellbeing, University of Newcastle, Newcastle, NSW, Australia; [e]Heart and Stroke Program, Hunter Medical Research Institute, NSW, Australia; [f]Hunter Stroke Service, Hunter New England Local Health District, Newcastle, NSW, Australia; [g]AdventHealth Research Institute, Neuroscience Institute, Orlando, FL, United States; [h]Department of Psychology, University of Pittsburgh, Pittsburgh PA, United States; and [i]PROFITH "PROmoting FITness and Health through physical activity" Research Group, Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Granada, Spain.

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Department and institution where the work was performed School of Health Sciences, University of Newcastle, Australia

Corresponding author at: School of Health Sciences, Heart and Stroke Program, Hunter Medical Research Institute, University of Newcastle, University Drive, Callaghan, NSW 2305 Australia. E-mail: coralie.english@newcastle.edu.au.

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many health benefits such as greater longevity and reduced risk of coronary heart disease, cardiovascular disease and stroke[7, 8] and may lower recurrent stroke risk[1, 2, 9]. Aerobic exercise increases cardiorespiratory fitness. While no large definitive trials have examined the effectiveness of exercise for secondary stroke prevention[10], the evidence to date is sufficient for international clinical guidelines in stroke to recommend exercise and/or physical activity interventions as part of secondary stroke prevention. Stroke guidelines align with population guidelines and recommend a minimum of 150 min per week (or 30 mins on most days) of moderate-to-vigorous physical activity[11-13], however, few people after stroke meet this recommendation[14]. There is evidence that post-stroke cardiorespiratory fitness may be improved with lower doses of aerobic exercise. A systematic review of 28 trials reported up to a 27% increase in cardiorespiratory fitness with doses of exercise lower than recommended guidelines (less than 30 min moderate intensity physical activity most days of the week[6]). People with stroke often have very low levels of physical activity and face barriers to participating in aerobic exercise including physical and cognitive impairment, and fatigue[15]. Therefore, understanding the minimum dose of aerobic exercise needed to improve fitness may provide an achievable first step to motivate people after stroke to start an exercise program.

The effects of specific dose parameters (frequency, intensity, time or type (FITT parameters))[16] on cardiorespiratory fitness after stroke are not clear. Few trials compare more than two intervention doses[17]. Consequently, low doses of aerobic exercise have not been systematically investigated after stroke[18]. To address this gap, dose-escalation (or Phase 1) trial designs, used primarily in pharmaceutical trials[19, 20], are an effective way to investigate several doses of an intervention or drug in a single trial. While such trials are designed primarily to determine dose safety and tolerability, preliminary evidence of dose efficacy might also be observed[21], and can inform future randomised controlled trials. In dose-escalation trials, a limited number of participants at each dose are enrolled, and doses are escalated in subsequent cohorts if the previous dose is deemed both safe and tolerable. Dose-escalation trials have been used previously in stroke intervention trials to determine the maximum tolerable dose of exercise[22] and the maximum safe and tolerable intensity of cardiorespiratory training early after stroke[23].

Recommendations from the Stroke Recovery and Rehabilitation Roundtable consensus papers[24, 25] indicate the need for more rigorous development of interventions in stroke recovery. As part of a careful, staged intervention development for a future exercise trial in stroke[26], we conducted a dose-escalation trial to test the effect of low doses of exercise manipulated by session duration (less than 30 min/d) on cardiorespiratory fitness in people after stroke. The research questions were:

For people who have had a stroke:

1 Is it feasible and safe to conduct a dose-finding study to test exercise doses? Specifically,

a Is it possible to recruit and retain participants?
b Are exercise testing methods feasible?
c Can target doses of exercise be adhered to?
d Is telehealth a safe and feasible means of providing supervised exercise sessions?

2 Is it possible to determine a minimal dose of exercise required to see clinically meaningful improvements in cardiorespiratory fitness?

Methods

Study design

A Phase I modified 3+3 dose-escalation study design[19] was used to determine the dose-response of an 8-week home-based telehealth-supervised aerobic exercise program on post-stroke cardiorespiratory fitness. People with stroke were recruited in four cohorts (n= 5 per cohort) via the Hunter Stroke Research Register, social and traditional media, databases of previous study participants who had agreed to be contacted for future studies, and by word of mouth. This study was approved by the Hunter New England Human Research Ethics Committee (HNEHREC Reference No: 16/10/19/4.09). All participants were provided with written information about the study aims and gave written informed consent. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000460303).

An initial assessment was undertaken as soon as possible after recruitment. Intervention sessions commenced the following week. Participants received telehealth-supervised exercises designed to increase cardiorespiratory fitness (peak oxygen consumption (VO_{2peak})) from an exercise scientist or a physiotherapist[27]. Once five participants in a cohort had completed both the intervention and final assessment, a new cohort (consisting the next five enrolled participants) commenced the study. If the previous dose was deemed tolerable according to pre-defined *dose escalation rules*, each subsequent cohort received a higher intervention dose than the previous cohort.

Dose escalation rules

Doses were escalated if less than a third of participants in the previous cohort reached a dose limiting threshold during the intervention[28]. The dose limiting threshold was reached if any of the following occurred: i) < 50% of the prescribed weekly exercise dose was not completed due to factors related to the intervention, ii) participants were unable to exercise for the required session duration, iii) participants withdrew from the study due to injury or illness that could be attributed to the intervention, or iv)

participants were unable to perform their normal activities of daily living following the exercise dose.

Outcomes were measured at four weeks to reflect the immediate effect of the intervention and at eight weeks to reflect longer-term outcomes. Outcome measures were collected by an experienced exercise scientist and research assistant. The nature of the dose escalation design meant that the assessors were not blinded to the dose the participant received. All assessments were conducted at the Human Performance Laboratory (University of Newcastle, Australia).

Participants

Community-dwelling stroke survivors were included if they were ≥ 18 years old, ≥ 3 months post-stroke, able to walk independently (score ≥ 3 on the Functional Ambulation Classification [FAC])[29], had suitable internet access and exercise space, and a responsible adult present during exercise sessions. They were excluded if they were unable to understand instructions in English, pregnant or planning to be pregnant during the study period, unable to understand 2-stage simple commands, had a self-reported current physical activity level ≥ 20 minutes 3 d/week at moderate intensity, were clinically diagnosed with an illness or conditions with known physical activity contraindications or limited their ability to complete the fitness assessments or intervention, unable to commit to all study requirements, or currently participating in either a stroke research trial or rehabilitation therapy focused on encouraging participation in physical activity. Participant characteristics were recorded at Week 0. These included: age, sex, time since stroke, stroke type, medications, comorbidities, self-reported physical activity (IPAQ)[30], stroke severity (Modified Rankin Screen (mRS))[31], physical impairment (Fugl-Meyer lower limb assessment)[32] walking ability (FAC)[29] and cognitive ability (Montreal Cognitive Assessment (MoCA))[33].

Intervention

Participants underwent an 8-week telehealth-supervised exercise program designed to increase cardiorespiratory fitness (see Supplementary material for detailed information of the intervention described using the template for intervention description and replication (TIDieR) checklist[34]). The exercise program consisted of thrice-weekly sessions, with exercise duration varying by dose, ranging from 10 min (Dose 1) up to 25 min (Dose 4) excluding warm up and cool-down periods.

Intervention dose parameters

i Frequency: 3d/week.
ii Intensity: Moderate-vigorous[35] (55-85% peak heart rate (HR_{peak}), determined during baseline fitness assessments, or at a rating of perceived exertion (RPE) between 11 and 16[36]. Heart rates were monitored using a pulse oximeter (Crucial Medical Solutions Model CMS50DL) or heart rate monitor (Garmin Forerunner 25).
iii Time (session duration): Varied by dose: 10 min (Dose 1), 15 min (Dose 2), 20 min (Dose 3) and 25 min (Dose 4).
iv Time (program length): 8 weeks.
v Type Predominantly bodyweight exercises. Typical exercises are shown in the Supplementary material Table S2.

The exercise program included exercises known to be effective in increasing cardiorespiratory fitness in a similar population in a previous study[37]. Exercises were adapted to account for participants' initial fitness, degree of disability and preferences. Within-session exercise interval lengths were increased, and recovery periods decreased steadily over the 8 weeks in line with progressive overload principles[38]. Prior to each session, resting heart rate was monitored and a wellness check conducted to determine whether participants had any current illnesses, injuries, or soreness. Exercise sessions were terminated or modified if any contraindications to exercise were observed[16] or if the participant requested.

Outcome measures

The primary research question was whether conducting a dose-finding study to test exercise doses in people with stroke was feasible and safe. To assess feasibility, we measured the time taken to recruit the target sample *(recruitment)*, the percentage of participants who completed the intervention and all assessments *(retention)*, the percentage of participants able to complete the exercise testing protocol *(feasibility of testing methods)* and the percentage of participants who achieved the target exercise dose *(adherence to target doses)*. To assess safety, we recorded number and type of adverse events.

The secondary research question aimed to determine the minimum dose of exercise required to see clinically meaningful improvements in cardiorespiratory fitness. A specific exercise dose was deemed efficacious if ≥ two-thirds of participants in the cohort increased VO_{2peak} from Week 0 to Week 8 by more than 2mL/kg/min (the minimum response criterion). This minimum response criterion was chosen as it i) is the magnitude of change typically reported in aerobic training trials in stroke[6], ii) represents the mid-point of the accepted minimal clinically important difference in cardiorespiratory fitness (1 to 3 mL/kg/min)[39-41], and iii) is above expected measurement error[42, 43]. VO_{2peak} was defined as the highest VO_2 (measured over a 15s epoch) recorded during either the 6-minute walk test (6MWT) or the graded exercise test (GXT), whichever was the greatest.

Measures of fitness

The testing order at each assessment was: i) resting heart rate and blood pressure (measured after a minimum of 5 min seated rest using a Connex® ProBP™ 3400 Digital Blood Pressure Device (WelchAllyn, USA)), ii) anthropometric measures (height, weight, hip and waist girth, and body mass index (BMI) using standardised methods[44]. iii) walking speed over the middle 10m of a 14m walkway (self-selected and fastest)[45], iv) 6MWT[46] to measure walking capacity, VO_{2peak} and HR_{peak}, and v) a cycle ergometer GXT (VO_{2peak} and HR_{peak}). Participants rested for a minimum of 20 min between the 6MWT and the GXT.

6MWT: The 6MWT test was conducted in accordance with the American Thoracic Society standards[46] using a walkway distance of 20m and any usual walking aids and/or orthoses. RPE was recorded immediately post-test.

GXT: Participants pedalled an electronically braked cycle ergometer (Monark 928 G3) at 20W (target cadence 60 rpm) for 3 min. Power output then was increased 10W every 30s until volitional fatigue or any contraindications[16] were observed. Reason for stopping, peak power ($Power_{peak}$ [W]), total time (Duration [s]) and final RPE were recorded.

Metabolic Measures: Breath by breath measures of ventilation, VO_2 and VCO_2 were collected throughout the 6MWT and the GXT using a portable (weight 800g) open-circuit spirometry system (K5, COSMED, Italy) worn on the participant's back. Calibration occurred immediately prior to each test according to the manufacturer's specifications. Data were processed using Omnia (Ver1.6) software. Metabolic variables were averaged in 15s epochs. A portable 12-lead echocardiogram system (Quark T12, COSMED, Italy) was used to continuously monitor heart rhythm to ensure participant safety and to determine HR_{peak}. Capillary blood was sampled for lactate concentration (mMol/L) prior to, and at 1- and 5-min post-test (Lactate Scout portable analyser (EKF Diagnostics, Germany)). Lac_{peak} was the highest measured concentration post-exercise. Maximal effort during fitness assessments was confirmed if any of the following occurred i) $HR_{peak} \geq 85\%$ age-predicted maximum (206.9-(0.67 x Age)[47]; ii) respiratory exchange ratio (RER) ≥ 1.05[48, 49]; iii) $Lac_{peak} \geq 4$mMol/L[48].

Data analyses

Descriptive statistics including means and standard deviations were calculated for the demographic and outcome data. We calculated mean differences and 95% confidence intervals between baseline and post-intervention values.

Results

Of the 66 people screened, 39 (59%) were eligible, 15 declined to participate and n = 24 were included (Fig. 1). Three participants (13%) withdrew prior to the second week of intervention and one participant failed to achieve VO_{2peak} at baseline. All were replaced by the next available participant. A total of 4 doses were tested. The first 5 participants received Dose 1 (the lowest dose of exercise; duration 10 min). As the dose-limiting threshold was not met for any participants or cohorts, enrolment continued, with subsequent participant cohorts receiving (in order) Dose 2 (n=5, 15 min), Dose 3 (n=5, 20 min) and Dose 4 (n=5, 25 min).

Participant characteristics

Baseline characteristics of participants who completed the intervention (n=20) are shown in Table 1 and were similar across cohorts. The mean (SD) age of participants was 62[11] years, and 12 (60%) were male. The mean time since stroke was 8[7] years. All participants were able to walk independently (FAC score $\geq$ 4), with a mean self-selected walking speed of 1.1 (0.4) m/s, but 16 (80%) scored 2 or 3 on the mRS indicating mild or moderate stroke-related disability. Most (n=19, 95%) had at least one cardiovascular risk factor (resting blood pressure >140/90 mmHg, BMI >30 km/m^2, waist circumference >94cm (males) or >80cm (females), or self−reported physical activity <150min/week), and 12 (60%) had more than two risk factors.

Feasibility

Participant recruitment and retention

Recruitment duration (n=24) was 17 months. Reasons for non-eligibility are described in Fig. 1 and included not having someone able to provide in-person supervision during the telehealth supervised exercise sessions, self-reported current physical activity level $\geq$ 20 min 3 d/week at moderate intensity or diagnosed with an illness or condition which had known physical activity contraindications or limited their ability to complete the fitness assessments or intervention. The 15 people who declined to participate did not provide a reason, and 2 of the 4 participants who were replaced had pre-existing conditions affecting their ability to exercise and withdrew voluntarily. Twenty participants (100%) completed the 8-week intervention. Of these, 18 (90%) completed all assessments.

VO_{2peak} data was obtained from 57/60 (95%) assessments. Missing data were imputed from the previous assessment (last value carried forward) on three occasions: one participant was unavailable at Week 4 assessment; two participants did not complete the Week 8 graded exercise test (one due to medical concerns and one due to equipment failure).

Adherence to target exercise dose

Target exercise sessions were well adhered to (Table 2) with 12 (60%) participants completing all sessions and a

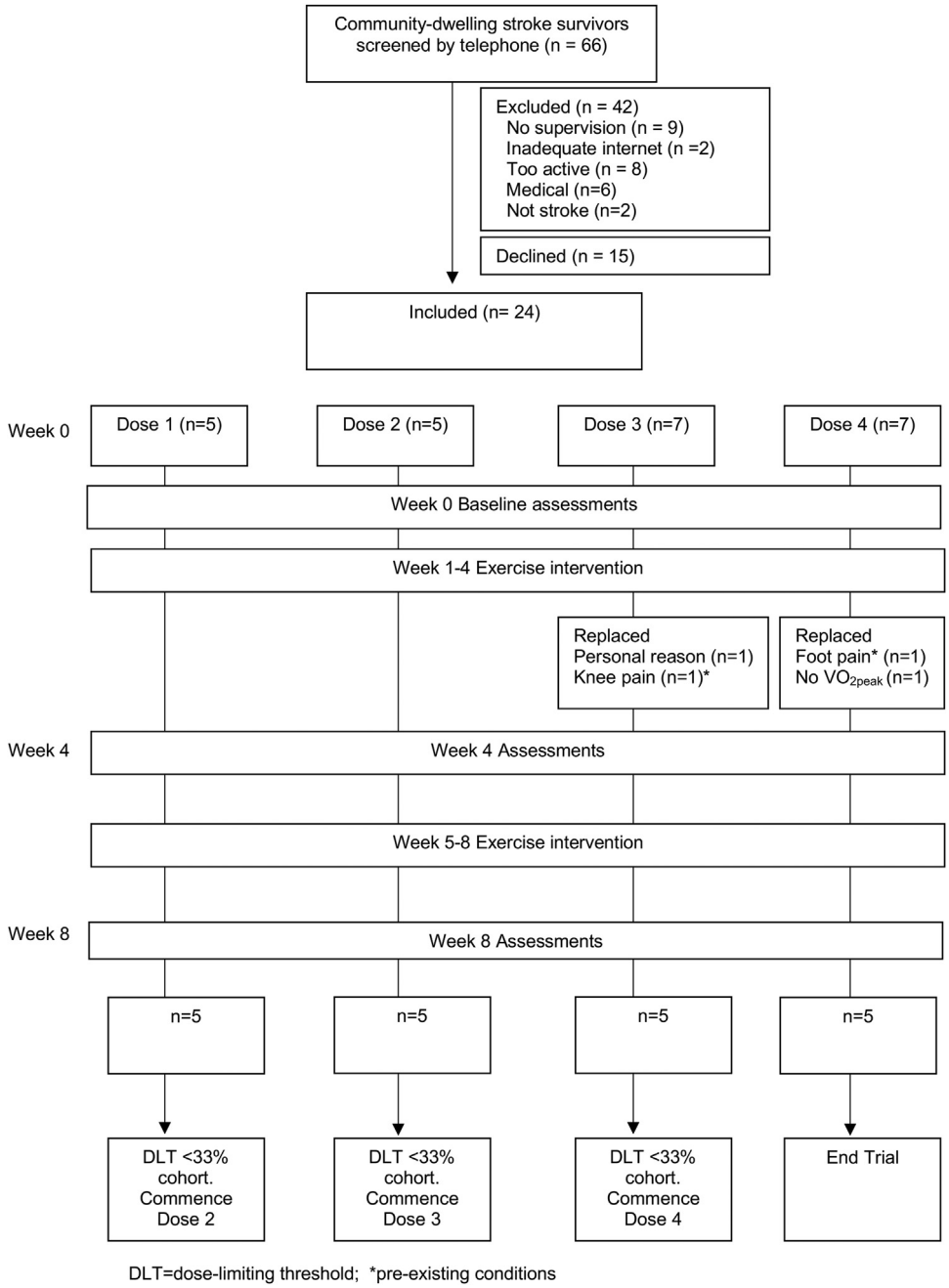

Fig. 1. *Design and flow of participants through trial.*

further 5 (25%) completing 23/24 sessions. For parameters of exercise dose, > 90% of sessions were completed (*frequency*), and all participants achieved the desired *program length* of 8 weeks. With regards to *intensity*, the mean %HR_{peak} (SD) for each dose cohort was between 71[11] and 82[9] and the target HR (55-85% HR_{peak}) was achieved (n=17; 85%) or exceeded (n= 3; 15%) by all participants. The mean RPE across all exercise sessions was >13 (i.e. vigorous or high intensity[35]). We were able to successfully manipulate the exercise dose by meeting target *session durations*.

Safety and feasibility of telehealth mode of exercise delivery

One adverse event (a fall requiring medical attention for a laceration) occurred during the intervention. The participant resumed exercise at the next scheduled session. A total of 455 out of 480 (95%) exercise sessions were delivered, 388 (85%) via real-time video conferencing, 20 (5%) by phone, 16 (4%) by combination of phone and video conferencing, and the remainder (6%) with face-to-face supervision (carer or trial staff). Other metrics for the

Table 1. *Baseline characteristics of participants.*

Characteristic	Dose 1(n = 5)	Dose 2(n=5)	Dose 3(n=5)	Dose 4(n=5)	All(n=20)
Age *(y)*, mean (SD)	61 (9)	64 (7)	61 (11)	60 (17)	62 (11)
Sex, *n* male (%)	4 (80)	3 (60)	2 (40)	3 (60)	12 (60)
Stroke Type, *n* (%)					
Haemorrhagic	3	2	1	2	8 (40)
Ischemic	0	2	4	3	9 (45)
Unknown	2	1	0	0	3 (15)
Stroke side, *n* Right/Left/Unknown	2/1/2	3/2/0	2/2/1	2/2/1	9/7/4
Time since stroke *(y)*, mean (SD)	10 (5)	5 (3)	8 (7)	8 (11)	8 (7)
Stroke-related disability (mRS)					
Score 0 − 1 (no significant disability) *n* (%)	1	1	2	0	4 (20)
Score 2 (slight disability) *n* (%)	2	1	1	4	8 (40)
Score 3 (moderate disability) *n* (%)	2	3	2	1	8 (40)
Stroke impairment					
FM_LL mean (SD) (0-34)	26 (10)	24 (8)	31 (4)	26 (7)	27 (7)
Cognition					
MoCA (0 to 30)	26 (2)	26 (2)	24 (5)	23 (3)	25 (3)
Walking Ability					
Speed, self-sel *(m/s)*, mean (SD)	1.0 (0.3)	0.9 (0.5)	1.4 (0.3)	1.1 (0.2)	1.1 (0.4)
FAC					
Score = 4 *n* (%)	0	2	0	0	2 (10)
Score = 5 *n* (%)	5	3	5	5	18 (90)
Living Arrangement					
At home, *n* yes (%)	5	5	5	5	20 (100)
With others, *n* yes (%)	5	4	5	4	18 (90)
Co-morbidities, *n*					
Hypertension/T2D/CVD	2/1/1	4/1/2	2/3/3	3/0/1	11/5/7
Beta-blockers, *n* yes (%)	1	2	1	2	6 (30)
Physical Activity					
Self-reported, (*min/wk*) mean (SD)	50 (75)	54 (80)	36 (53)	102 (83)	60 (72)

mRs= modified Rankin Score; FM_LL= Fugl-Meyer lower limb; FAC= Functional Ambulation Classification score; MoCA=Montreal Cognitive Assessment;T2D=Type 2 Diabetes. CV= cardiovascular disease

feasibility of telehealth delivery are reported elsewhere (n=21)[27].

Effect of exercise dose on cardiorespiratory fitness

All doses were deemed tolerable (no participant reached the dose-limiting threshold). No doses met our criteria for efficacy (≥ two-thirds of participants exceeding the minimum response criteria of >2ml/kg/min increase in $VO_{2peak.}$). Individual data for VO_{2peak} (mL/kg/min) at Week 0 and Week 8 for all participants are shown in Table 3, and group data for VO_{2peak} and associated fitness measures in Table 4.

Discussion

We have shown it is possible to recruit and retain community-dwelling stroke survivors in an exercise dose-finding study aimed at determining the effect of dose (session duration) on cardiorespiratory fitness. Participation

Table 2. *Adherence to target dose of exercise.*

	Session duration, *min**	Frequency, *completed sessions*n (%)	Program length, *weeks*mean (SD)	Intensity	
				%HRpeak *mean (SD)***	RPE *mean (SD)***
Dose 1	10 min	22 (92)	8 (0)	82 (9)	15 (2)
Dose 2	15 min	23 (96)	8 (0)	71 (11)	16 (1)
Dose 3	20 min	23 (96)	8 (0)	79 (11)	13 (1)
Dose 4	25 min	23 (96)	8 (0)	73 (6)	15 (1)

*All sessions met duration targets, but time in sessions was not formally recorded
**averaged over Week 3 to Week 8

Table 3. *Effect of exercise dose on cardiorespiratory fitness.*

	VO_{2peak} *(mL/kg/min)*		Change over time, mean difference (95% CI)
Participant	Week 0	Week 8	Week 8 minus Week 0
Dose 1			
1	10.1	15.3	5.2
2	8.4	9.7	1.3
3	15.4	13.6	-1.8
4	14.0	18.5	4.5
5	20.0	19.1	-0.9
Mean (SD)	13.6 (4.6)	15.3(3.8)	1.7 (-2.3-5.6)
Minimum response criterion exceeded, *n* (%)	2 (40)		
Dose 2			
6	20.1	29.2	9.1
7	13.5	13.8	0.3
8	15.4	14.7	-0.7
9	17.8	18.9	1.1
10	16.0	17.3	1.3
Mean (SD)	16.6 (2.5)	18.8 (6.2)	2.2 (-2.6-7.1)
Minimum response criterion exceeded, *n* (%)	1 (20)		
Dose 3			
11	17.6	18.1	0.5
12	19.5	23.1	3.6
13	16.8	22.4	5.6
14	13.6	15.3	1.7
15	10.8	14.4	3.6
Mean (SD)	15.7 (3.5)	18.7 (4.0)	3.0 (0.6-5.4)
Minimum response criterion exceeded, *n* (%)	3 (60)		
Dose 4			
16	18.5	20.6	2.1
17	9.5	11.3	1.8
18	12.4	11.6	-0.8
19	19.2	18.0	-1.2
20	16.0	18.4	2.4
Mean (SD)	15.1 (4.1)	16.0 (4.3)	0.9 (-1.3-3.0)
Minimum response criterion exceeded, *n* (%)	2 (40)		

required three laboratory visits and thrice-weekly telehealth supervised exercise sessions performed at moderate-to-vigorous intensity over 8 weeks. Furthermore, we demonstrated that the methods we used to assess outcomes were feasible, and participants were able to adhere to the target exercise doses. We also demonstrated that delivering supervised exercise via telehealth was safe for the participants involved. We did not demonstrate clinically meaningful improvements in cardiorespiratory fitness in sufficient participants within a cohort for any of the doses assessed. Consequently, we were not able to identify a minimum exercise dose.

While we found it was feasible to recruit to this study, there were several challenges with only 24 (36%) participants successfully recruited to the study. Of the 66 potential participants screened, 15 (23%) declined and a further 27 (41%) were excluded. The two most frequent reasons for exclusion were not having a person available at home to supervise exercise sessions or being too physically active (i.e., those who self-reported more than 20 min of moderate-to-vigorous physical activity (MVPA) for 3 or more d/week). We were concerned that providing exercise sessions via telehealth to people with stroke who often have balance impairment may increase the risk of falls. To mitigate safety risk, we required participants to have someone at home able to supervise their exercise sessions. However, we were able to deliver 455 exercise sessions with only one adverse event (fall with minor laceration). The low rate of adverse events suggests that the requirement for supervision may not have been necessary. It is of course important that any future trials of telehealth delivered exercise sessions continue to carefully monitor and record adverse events. We specified the upper limit of regular physical activity (> 20 min MVPA 3 days/week) as an exclusion criterion as we aimed to recruit participants with low baseline fitness. It is not uncommon for trials of exercise interventions to attract volunteers who are already regular exercisers. It is not surprising that the same phenomenon occurred in our trial, given that our trial aimed to evaluate exercise dose,

Table 4. *Cardiorespiratory fitness and walking capacity.*

Outcome	Week 0				Week 8				Difference within doses Week 8 - Week 0			
Dose	1	2	3	4	1	2	3	4	1	2	3	4
Peak $VO2_{peak}$ (mL/kg/min)	13.6(4.6)	16.6(2.5)	15.7(3.4)	15.1(4.0)	15.3(3.9)	18.8(6.1)	18.7(4.0)	16.0(4.3)	1.7(-2.3 to 5.6)	2.2(-2.6 to 7.1)	**3.0(0.6 to 5.4)**	0.9(-1.3 -to3.0)
$VO2_{peak}$ (L/min)	1.01(0.19)	1.47(0.52)	1.27(0.40)	1.37(0.39)	1.17(0.27)	1.67(0.69)	1.52(0.43)	1.47(0.48)	0.16(-0.18 to 0.49)	0.19(-0.20 to 0.58)	**0.25(0.07 to 0.43)**	0.10(-0.14 to 0.34)
GXT $VO2_{peak}$ (mL/kg/min	13.4(4.8)	16.5(2.6)	15.5(3.7)	14.6(4.5)	14.4(4.7)	17.9(4.4)	18.4(4.4)	15.8(4.5)	1.0(-2.8 to 4.9)	1.4(-1.2 to 4.0)	**2.8(0.4 to 5.2)**	1.2(-0.6 to 3.0)
$VO2_{peak}$ (L/min)	0.99(0.19)	1.47(0.52)	1.26(0.42)	1.32(0.42)	1.09(0.28)	1.59(0.63)	1.50(0.46)	1.44(0.46)	0.10(-0.22 to 0.42)	0.13(-0.09 to 0.35)	**0.24(0.06 to 0.41)**	0.12(-0.06 to 0.29)
Duration (s)	393(86)	379(184)	445(77)	395(87)	393(83)	454(163)	470(96)	419(71)	0(-40 to 40)	75(-4 to 154)	25(-13 to 63)	24(-3 to 50)
RER	1.49(0.15)	1.18(0.08)	1.30(0.08)	1.08(0.07)	1.41(0.18)	1.22(0.11)	1.31(0.05)	1.10(0.14)	-0.08(-0.35 to 0.19)	0.04(-0.31 to 0.11)	0.01(-0.05 to 0.07)	0.02(-0.11 to 0.16)
$Lactate_{peak}$ (mMol/L)	7.4(4.3)	6.5(3.9)	6.9(1.9)	5.7(2.2)	7.9(4.0)	8.0(3.2)	7.4(2.4)	4.5(1.3)	0.5(-4.4 to 5.5)	1.5(-2.3 to 5.2)	0.5(-1.5 to 2.5)	-1.3(-3.0 to 0.5)
$Power_{peak}$ (W)	96(29)	96(54)	112(28)	96(27)	96(29)	116(58)	120(29)	102(27)	0(-12 to 12)	**20(11 to 29)**	8(-5 to 21)	**6(0 to 13)**
6MWT $VO2_{peak}$ (mL/kg/min)	11.1(2.2)	15.22.4	13.1(2.0)	13.7(3.9)	12.9(2.2)	17.0(7.1)	15.5(3.4)	14.7(4.0)	1.9(-0.5 to 4.3)	1.8(-4.4 to 7.9)	2.4(-0.2 to 5.0)	0.9(-1.0 to 2.9)
$VO2_{peak}$ (L/min)	0.84(0.13)	1.33(0.40)	1.05(0.25)	1.25(0.42)	1.01(0.30)	1.51(0.70)	1.25(0.33)	1.37(0.50)	0.17(-0.07 to 0.41)	0.17(-0.31 to 0.66)	**0.20(0.00 to 0.40)**	0.12(-0.12 to 0.35)
Distance (m)	366(85)	323(179)	422(87)	362(79)	379(77)	369(214)	447(106)	375(83)	12(-6 to 31)	46(-20 to 111)	25(-14 to 65)	13(-17 to 42)

Mean (SD) of dose groups; mean (95% CI) difference within groups for outcomes by dose. Significant findings are bolded.
Peak = highest VO_2 (15s epoch) recorded during either GXT or 6MWT at each assessment point

rather than being specifically designed to encourage people to be physically active.

We chose a dose-escalation study design to assess the safety and efficacy of a number of exercise doses in a timely fashion, with the broader aim being to provide evidence for an appropriate dose(s) to test in a fully-powered randomised controlled trial. This approach is in line with the recommendations from the Stroke Recovery and Rehabilitation Roundtable consensus papers[24, 25] that indicate the need for more rigorous development of interventions in stroke recovery. We found the dose-escalation design was feasible to implement.

We were not able to determine a minimum effective dose for exercise, which may have been due to the small cohort sizes involved. The standard of 67% meeting the minimum response criterion with a cohort of 5 meant that 4 (80%) participants were required to meet the criterion. While a number of individual participants in each dose cohort did demonstrate an increase in VO_{2peak} greater than the minimum response criterion, the variation in responses may have been affected by the wide range in exercise intensity used in this study (55-85% HR_{peak}). It is possible that a future study with larger cohort sizes and a narrower range of target intensity may allow us to determine a minimum effective dose of exercise to improve cardiorespiratory fitness in people with stroke. It is also possible that our program length of 8 weeks was too short to see clinically significant gains in fitness. Previous reviews of exercise interventions for people with stroke have suggested that exercise program lengths of at least 4 months may be required to be effective[50].

Low physical activity is one of the top 10 risk factors for first stroke and has been shown to be an independent risk factor for recurrent stroke[9]. The Australian and New Zealand Living Clinical Guidelines for Stroke Management recommend people with stroke receive interventions to reduce recurrent stroke risk factors that includes exercise training[12]. However, the barriers for exercise engagement for people with stroke are well known and include lack of self-efficacy, concerns about safety, transport, and the desire for exercise sessions to be supervised by health professionals with expertise in stroke[51, 52]. Supervision of exercise sessions is an essential component for successful exercise trials in people with stroke[53]. The Covid-19 pandemic brought into sharp focus the need for telehealth models of service delivery. Our study has shown that it is feasible and safe to provide supervised exercise training to people with stroke via telehealth.

Strengths and limitations

Our study has both strengths and limitations. By manipulating one dose parameter (session duration) while controlling all others, we were able to compare four doses of exercise in a single trial. We increased the likelihood of eliciting a maximal effort during fitness

assessments by including both a GXT and a 6MWT. However, the dose-escalation design introduces elements of potential bias as participants were systematically, but not randomly, allocated to groups and outcome assessments were unblinded. In addition, the small sample size for each dose may have affected the results, and the length of the intervention period may not have been sufficient to allow for many physiological adaptations. We included only ambulant people with mild-moderate impairments who were, on average, many years post-stroke, and therefore the results may not be generalisable beyond this group.

Future Studies

The results from this study were used to inform a larger randomised controlled trial[26] comparing the effect of telehealth diet and exercise interventions on secondary stroke prevention. As part of this trial the safety and feasibility of providing telehealth-supervised exercise sessions without home supervision will be assessed.

Conclusion

In conclusion, while it is feasible and safe to use a dose-escalation design to assess a number of low doses of exercise in a single trial, it was not possible to determine a minimum dose that increased cardiorespiratory fitness.

Ethics approval

This study was approved by the Hunter New England Human Research Ethics Committee (HNEHREC Reference No: 16/10/19/4.09).

Clinical Trial Registration

Australian New Zealand Clinical Trials Registry (Trial ID: ACTRN12617000460303).

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Disclosures

NIL

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Professor Coralie English reports financial support was provided by Stroke Foundation Australia. Professor Coralie English reports financial support was provided by National Heart Foundation of Australia. Professor Coralie English reports a relationship with Stroke Foundation Australia that includes: board membership.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2023.107190.

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