An exploration of low doses of exercise on cardiorespiratory fitness in people with chronic stroke

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provided in establishing the Stroke Research Register (and Gillian Mason in particular). Without this, our ability to find participants for clinical trials in stroke would be incredibly difficult. I would also like to thank Prof Trevor Russell for the in-kind support to the telehealth platform used in my study.

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I would like to also express my overwhelming gratitude to all the participants who volunteered to take part in my studies. All of you live with the consequences of stroke, and without your valuable contribution, good humour and willingness to volunteer, this project would never have been attempted. You offered your time, you trained your hearts out, provided your valuable feedback and gave us more than your pound of sweat. May your health continue to improve, and your journey beyond stroke be happy.

To my parents Pam and Gal. Mum, I finally understand why you loved being a physio to 'old people who have had a stroke'. The rewards from helping people go far beyond the treatment, and your actions have had a huge impact on many stroke survivors' lives.

To my Dad Gal, who passed away during my candidature from the devastating effects of stroke-related vascular dementia. If only we knew more when you had your first TIA things may have been different. I dedicate this thesis to your memory.

And finally to my beautiful family. Dave, you have encouraged me every step of the way. It was your idea completely to cajole me back towards academia, and you convinced me I could to do a PhD in an area I essentially knew nothing about. You have selflessly allowed me the freedom to pursue my studies, have cooked every delicious meal along the way, and convinced me to stick with it when my energy flagged. I love you with all my heart. To my darling daughter Alannah. I hope that I have shown you that you are never too old to pursue excellence and find a new path in life. I hope that that I have been a role model for you and your friends, and that my experiences may inspire you in your academic path. I love you too.

Publications arising from this thesis

This thesis is presented with the inclusion of four papers. I am the lead author on all papers. At the time of submission, one of these papers (Chapter 3) is published in a peer-reviewed journal, two papers (Chapters 4 and 6) have been submitted to peer reviewed journals and one (Chapter 5) is being prepared for submission.

Manuscripts in peer-reviewed journals: Published

1. Galloway, M, Marsden, DL, Callister, R, Erickson, K, Nilsson, M, English, C. What Is the Dose-Response Relationship Between Exercise and Cardiorespiratory Fitness After Stroke? A Systematic Review, *Physical Therapy*, Volume 99, Issue 7, July 2019, Pages 821–832

Manuscripts in peer-reviewed journals: Under review.

1. Galloway M, Marsden DL, Callister R, Erickson KI, Nilsson M, English C. A preliminary study of low doses of moderate-vigorous exercise on cardiorespiratory fitness in chronic stroke survivors. A Phase I dose-escalation trial. *Manuscript submitted for review to Disability and Rehabilitation*
2. Galloway M, Marsden DL, Callister R, Erickson KI, Nilsson M, English C. Telehealth delivery of exercise aimed at improving cardiorespiratory fitness is feasible for community-dwelling people after stroke. *Manuscript submitted for review to the International Journal of Telerehabilitation.*

Presentations arising from this thesis

During my candidature, I presented results arising from this thesis at four conferences, and have an abstract accepted at one other. This resulted in three oral and two poster presentations. I was also invited to present at four research seminars and one community event and am a co-author on three other conference presentations for work that has built on my thesis findings. Details of all presentations are as follows:

International Conference presentations

1. **Galloway, M**, Marsden, DL, Callister, R, Erickson, K, Nilsson, M, English, C. The dose-response of aerobic exercise after stroke on cardiorespiratory fitness: a phase 1 dose-escalation trial. European Society of Stroke Conference: Milan, Italy, 22-24 May 2019. E-Poster

National Conference presentations

2. **Galloway, M**, Marsden, DL, Callister, R, Erickson, K, Nilsson, M, English, C. Determining the minimum dose of exercise required to improve cardiorespiratory fitness in stroke survivors: Protocol for the ExDose Trial. *Smart Strokes Conference. Gold Coast, Australia. August 10-11 2017.* Poster presentation
3. **Galloway, M**, Marsden, DL, Callister, R., Erickson, K, Nilsson, M. English, C. The effects of changing exercise dose parameters on cardiorespiratory fitness in people after stroke: a systematic review (2018). *Stroke 2018 Conference: Sydney Australia. August 7-10 2018.* Oral presentation. Published in *International Journal of Stroke 2018, 13, 17-17.*
4. **Galloway, M**, Marsden, DL, Callister, R., Erickson, K, Nilsson, M, English, C. Cardiorespiratory fitness training sessions delivered via telehealth are safe, feasible and acceptable for community-dwelling stroke survivors. *Australian Telehealth Conference: Brisbane, Australia, April 3-4 2019.* Oral Presentation.
5. **Galloway, M**, Marsden, DL, Callister, R., Erickson, K, Nilsson, M, English, C. The dose-response of aerobic exercise after stroke on cardiorespiratory fitness: a phase 1 dose-escalation trial. Smart Strokes 2019. *Hunter Valley, Australia August 8-9 2019*. Abstract accepted for oral presentation.

Conference presentations (co-authored)

1. Ramage E, Burke **M, Galloway,** Janssen H, Lynch E, Marsden D, Patterson A, Pollack M, Said C, English C. Knowledge translation through co-design: The development of an exercise intervention for stroke survivors. Accepted for presentation at the *Smart Strokes Conference, Hunter Valley, August 2019*
2. Ramage E, Burke **M, Galloway**, Janssen H, Lynch E, Marsden D, Patterson A, Pollack M, Said C, English C. Complex intervention design in stroke. A knowledge translation approach highlighting the impact of stakeholder involvement. Accepted for presentation at the *Stroke Society of Australia Conference, Canberra, September 2019*
3. Ramage E, Burke **M, Galloway**, Janssen H, Lynch E, Marsden D, Patterson A, Pollack M, Said C , English C. Exercise delivered via telehealth to reduce secondary stroke risk needs the right equipment, resources and clinician training to optimise success. Accepted for presentation at the *Australian Physiotherapy Conference, 17-19th October 2019*

Research seminars and Events

1. **Galloway, M**, Marsden, DL, Callister, R, Erickson, K, Nilsson, M, English, C. Exercise dose response in stroke survivors. *University of Newcastle Health Science Research Day, 2016.* Poster presentation.
2. **Galloway, M**, Marsden, DL, Callister, R, Erickson, K, Nilsson, M, English, C. Investigating the minimum dose of exercise required to improve cardiorespiratory fitness in stroke survivors. *University of Newcastle Physiotherapy Research Seminar. 17 October 2017*. Oral presentation.
3. **Galloway, M**, Marsden, DL, Callister, R, Erickson, K, Nilsson, M, English, C. Fitness and exercise after stroke: is twice as much twice as good, or, is half as much not half bad? *Centre for Research Excellence for Stroke Rehab and Brain Recovery 5 min slide competition. HMRI, Newcastle, Australia. 8 August 2017*. Oral Presentation

Community Events

1. **Galloway, M.** The ExDose Study. Research into clinical telehealth in stroke rehabilitation. *Centre for Research Excellence for Stroke Rehabilitation and Brain Recovery workshop and public forum. Newcastle, Australia. August 7 2019* Invited speaker.

Awards

Throughout my candidature, I have been supported by an Australian Postgraduate Award Scholarship ($26,288 p.a. awarded in December, 2015) and a University of Newcastle/ HMRI Barker Family Top-up Scholarship ($14,000 awarded August 2017).

As chief investigator I was successful in obtaining a grant from the Stroke Foundation ($19,863.30) in December 2016 to support the conduct of the primary study included in this thesis.

Declarations

Statement of Originality

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

Signed:

Name: Margaret Galloway Date: 23 July 2019

Contribution statement

The body of work presented in this thesis has produced four papers. I was the sole PhD student responsible for all studies included as part of this thesis, and I contributed to all aspects of this project. A summary of my contributions and involvement is outlined at the beginning of each chapter.

Acknowledgment of authorship

I hereby certify that the work embodied in this thesis contains one published paper and scholarly work of which I am a joint author. I have included a written declaration endorsed in writing by my supervisor, attesting to my contribution to the joint publication/s/scholarly work.

Signed:

Name: Margaret Galloway Date: 23 July 2019

By signing below I confirm that Margaret Galloway contributed to the research question, the literature search and led the title, abstract and full-text screening of articles, data extraction, quality appraisal, and synthesis of results, and the preparation of the manuscript for the following publication.

Galloway, M., Marsden, D., Callister, R., Erickson, K., Nilsson, M., English, C. What Is the Dose-Response Relationship Between Exercise and Cardiorespiratory Fitness After Stroke? A Systematic Review, *Physical Therapy*, Volume 99, Issue 7, July 2019, Pages 821–832

[Signature of Supervisor]

Name: A/Prof Coralie English Date: 23 July 2019

Common Abbreviations

Abbreviation	Meaning
6MWT	Six Minute Walk Test
ACSM	American College of Sports Medicine
CI	Confidence Interval
FAC	Functional Ambulation Classification
FITT	Frequency, Intensity, Time, Type
FM_LL	Fugl Meyer Lower Limb
GPS	Global Positioning Sensors
GXT	Graded Exercise Test
HIIT	High Intensity Interval Training
HR	Heart Rate
HRR	Heart Rate Reserve
Lac	Lactate Concentration
mRS	Modified Rankin Score
MCID	Minimal Clinically Important Difference
RCT	Randomised Controlled Trial
RER	Respiratory Exchange Ratio

RPE	Rating of Perceived Exertion
SD	Standard Deviation
VE	Minute Ventilation
VCO_2	Carbon Dioxide Production
$VO2_{max}$	Maximal Oxygen Consumption
$VO2_{peak}$	Peak Oxygen Consumption

Terminology

"Stroke survivor": Throughout this thesis I have adopted "person first" language where possible, but to enhance readability I have sometimes chosen to use the term "stroke survivor". This is the preferred term for "people with stroke" in Australia, however it is understood that in other countries this may not be the case.

"Chronic Stroke": The accepted definition of chronic stroke is 6 months post-stroke,[1] however one participant included in my main study (Chapter 4) was 5 months post-stroke at enrolment and all others were greater than 6 months. I therefore chose to use the term chronic stroke to describe my population in all studies involving this cohort of participants.

Definitions

Term	Meaning of terms adopted throughout this thesis
Acute Stroke	Less than 6 months post-stroke
Aerobic Exercise	Physical activity that increases the heart rate and the body's use of oxygen
Chronic stroke	More than 5 months post-stroke
Daily physical activity	Physical activity measured during waking hours over a 24-hour period
Exercise	Structured physical activity aimed at increasing cardiorespiratory fitness
Habitual physical activity	Physical activity averaged over 3-7 days
Low-dose aerobic exercise	Exercise session durations less than 30 min
Physical activity	Any bodily movement produced by skeletal muscles that requires energy expenditure[2]
Minimal clinically important difference	The smallest improvement that patients perceive as beneficial
MVPA	Time spent in moderate-vigorous activity
Telehealth-supervised exercise sessions	Exercise sessions supervised via video-conferences, telephone calls, or both
Sedentary behaviour	Time spent sitting or lying

Thesis structure

This PhD is a hybrid thesis, including published and non-published papers. It is presented as a series of four manuscripts. The manuscript for the published paper[3] is included in Chapter 3, and a copy of the published paper included in the thesis Appendix. Two papers (Chapters 4 and 6) have been submitted to peer-reviewed journals, and the remaining chapter (Chapter 5) is being prepared for submission. As chapters 3, 4, 5, and 6 have been prepared as stand-alone papers, there is some duplication of information among chapters.

The structure of this PhD thesis is as follows:

Chapter 1	*Introduction:* An overview of the thesis topic, a summary of the background concepts, rationale and statement of the topic, concluding with the research questions to be answered and the hypotheses to be tested.
Chapter 2:	*Literature Review:* A review of the current scientific research regarding stroke and exercise focusing on risk factors for primary and secondary stroke, cardiorespiratory fitness and physical activity after stroke. It concludes with a review of the concept of exercise dose and dose-finding methodology.
Chapter 3:	*Systematic Review*: A systematic review of research that compares the effect of different doses of exercise on cardiorespiratory fitness after stroke, resulting in the following paper: Galloway, M., Marsden, D., Callister, R., Erickson, K., Nilsson, M., English, C. What Is the Dose-Response Relationship Between Exercise and Cardiorespiratory Fitness After Stroke? A Systematic Review. *Physical Therapy*, Volume 99, Issue 7, July 2019, Pages 821–832
Chapter 4:	*Dose-escalation trial:* A Phase I dose-escalation trial designed to determine the tolerability and preliminary efficacy of an 8-week home-based telehealth-supervised exercise program on post-stroke cardiorespiratory fitness, resulting in the following paper: *Galloway M., Marsden D., Callister, R., Nilsson, M., Erickson, K., English, C.* A preliminary study of low doses of moderate-vigorous exercise on

	cardiorespiratory fitness in people with chronic stroke. A Phase I dose-escalation trial (manuscript submitted for publication to *Disability and Rehabilitation*). The chapter also includes an extended discussion around the study design.
Chapter 5	*Physical activity and cardiorespiratory fitness:* A secondary analysis of data from the dose-escalation trial, focussing on the effect of regular exercise training on habitual and daily physical activity. *Galloway M., Marsden D., Callister, R., Nilsson, M., Erickson, K., English, C.* A home-based telehealth-supervised aerobic training program does not improve habitual physical activity in people with chronic stroke. (Manuscript in preparation).
Chapter 6	*Feasibility of telehealth-supervised exercise after stroke:* A study of the feasibility and level of satisfaction with home-based telehealth-supervised aerobic exercise training for people after stroke resulting in the following paper: *Galloway M., Marsden D., Callister, R., Nilsson, M., Erickson, K., English, C.* Telehealth delivery of exercise aimed at improving cardiorespiratory fitness is feasible for community-dwelling people after stroke. (Submitted for publication to the *International Journal of Telerehabilitation).*
Chapter 7	*Thesis discussion:* A summary of the key findings from each chapter, followed by an interpretation of the findings in light of current evidence and current practice. This chapter concludes with an outline of the steps that need to be addressed before implementation or adoption of these findings is possible.

Abstract

Background:

Low levels of cardiorespiratory fitness and physical activity are common after stroke, and can increase the risk of secondary stroke. Exercise training can increase cardiorespiratory fitness after stroke, however the minimal or optimal exercise dose to increase cardiorespiratory fitness is unclear. People with chronic stroke do not achieve the levels of physical activity recommended in current physical activity guidelines, and it is possible lower doses of exercise may be effective in increasing cardiorespiratory fitness.

Objective:

The primary aim of this thesis was to explore the effect of low doses of aerobic exercise on cardiorespiratory fitness and physical activity levels after stroke to determine if a minimum dose of exercise is required to improve cardiorespiratory fitness. The secondary aim was to assess the feasibility of delivering low-dose aerobic exercise to people after stroke via telehealth.

Methods:

To address these objectives I undertook four studies:

Study 1: I conducted a systematic review to synthesise the current evidence for the effects of different doses of exercise on cardiorespiratory fitness and walking capacity in people after stroke.

Study 2: I conducted a Phase I dose-escalation trial of low doses of aerobic exercise to determine the i) tolerability, preliminary efficacy and dose-response of low doses of aerobic exercise, and ii) effect of low-dose exercise on cardiorespiratory fitness, walking ability and quality of life on community-dwelling ambulant chronic stroke survivors. Four doses of exercise were assessed. 20 participants in consecutive cohorts (n=5 per cohort) received home-based telehealth-supervised aerobic exercise. The intervention frequency, program length and intensity were kept constant (3 d/week, 8-weeks, and moderate-vigorous [55-85% HR_{peak}]) and the doses varied by session duration (Dose 1 = 10 min, Dose 2 = 15 min, Dose 3 = 20 min, Dose 4 = 25 min)

We set *a priori* rules to determine dose-limiting thresholds and dose efficacy to guide the conduct of the dose-escalation trial. Doses were escalated if < 33% of a cohort reached a dose-limiting threshold. Doses were efficacious if ≥ 67% of a cohort increased peak oxygen consumption ($VO2_{peak}$) ≥ 2mL/kg/min.

Study 3: I undertook a secondary analysis of data collected in Study 2 to determine i) the effect the exercise intervention on physical activity levels and sedentary behaviour in people with chronic stroke during and after the exercise intervention, and ii) the relationship between changes in physical activity and changes in cardiorespiratory fitness.

Study 4: Participants in the exercise intervention in Study 2 were supervised by telehealth. The feasibility of, and level of satisfaction with home-based telehealth-supervised aerobic exercise training for people after stroke were assessed using participant feedback and data collected during exercise sessions by the exercise instructor.

Results:

Study 1. The review included 9 trials (n = 279 participants). Training at higher exercise intensities was associated with greater improvements in cardiorespiratory fitness (VO_{2peak}). Walking capacity increased with longer program length in most studies, however the effect of exercise intensity on walking capacity (6-min walk test) was unclear. No trials compared doses of different exercise training frequencies, different exercise session durations, or different types or modes of exercise training.

Study 2: Exercise doses ranging from 10 min up to 25 min/session were tolerable for all participants (no participants reached the dose-limiting threshold). Preliminary efficacy was not established for any doses. The mean improvement in cardiorespiratory fitness for the 20 min/session dose was 3.0 mL/kg/min, 95% CI 0.6 to 5.4, and this dose merits further investigation. In pooled data from all dose cohorts low-dose (short duration) exercise resulted in increased cardiorespiratory fitness (ΔVO_{2peak} = 1.9 mL/kg/min, 95% CI 0.7 to 3.2, walking capacity (Δ6-minute walk test = 25m, 95% CI 8 to 40) and self-rated health status (ΔEQ-VAS score = 9, 95% CI 3 to 15).

Study 3: 8 weeks of home-based supervised aerobic training had no effect overall on the level of habitual physical activity. Physical activity (steps/day) was 33% higher (mean difference 1675

steps/day; 95% CI: 840 to 2510) on training days compared to non-training days, and changes in physical activity (steps/day) were moderately associated with changes in cardiorespiratory fitness (VO_{2peak}) (r=0.44, p=0.05).

Study 4: Outcome feasibility measures for the telehealth-supervised exercise intervention were high from the perspective of both participants and researchers. Neither age, level of post-stroke impairment nor level of technical familiarity were associated with participants' level of satisfaction, and for eligible participants who enrolled, were not barriers to successfully participating in telehealth supervised exercise sessions.

Conclusion:

Low doses of home-based telehealth-supervised aerobic exercise for community-dwelling chronic stroke survivors were tolerable. Participants exercised at a moderate-vigorous intensity, 3 times per week for 8 weeks, and engaged safely and successfully in telehealth-supervised exercise sessions. The findings will be used to inform the development of an intervention for a Phase II trial of supervised exercise delivered via telehealth to reduce secondary stroke risk.

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