PeRsonalised Exercise for Priming Post-stroke (PREPP): Exploring intervention and outcome for clinical application

Ashcroft, Sarah

PeRsonalised Exercise for Priming Post-stroke (PREPP): Exploring intervention and outcome for clinical application

Submitted by:

Sarah Kate Ashcroft

BHlthSc(Sp&ExSc), MCEP

A thesis submitted in fulfilment of the requirements of the degree:

Doctor of Philosophy

Ph.D. with Publication

School of Allied Health

Australian Catholic University

Sydney, New South Wales, Australia

ABSTRACT

Stroke is a leading cause of disability and mortality worldwide, with more than 475,000 people currently living with lasting impairment in Australia including deconditioning and upper limb impairment. Neuroplasticity is considered a treatment target for stroke rehabilitation and recovery due to its association with improved prognosis and functional outcome. Exercise interventions may be utilised as a primer for motor rehabilitation post-stroke due to the potential to increase biomarkers of neuroplasticity such as Brain-Derived Neurotrophic Factor (BDNF). It is proposed that exercise interventions to increase BDNF concentration may be used as an adjuvant therapy to motor rehabilitation such as Constraint-Induced Movement Therapy (CIMT) to increase effectiveness. However, the optimal prescription and clinical application of exercise to increase BDNF concentrations have not been explored. The aim of this thesis was to explore exercise prescription and uptake post-stroke by 1) identifying optimal exercise training parameters, 2) investigating barriers and facilitators to the prescription and uptake of exercise in clinical practice, and 3) examining the relationship between commonly used outcome measures of neuroplasticity and upper limb function.

This thesis consists of four individual studies. The first study is a systematic review and meta-analysis that explored parameters of exercise prescription and their relationship to BDNF concentration in people with stroke. Seven electronic databases were searched for experimental or observational studies measuring changes in BDNF concentration after exercise in people with stroke. Meta-analyses demonstrated significant increases in BDNF concentration following a single session, and program, of high intensity aerobic exercise (e.g., High Intensity Interval Training [HIIT]). This study was published in the journal ‘Stroke’.

The second study was a mixed methods study that explored the barriers and facilitators to the use of HIIT post-stroke. People with stroke and health professionals who work in stroke rehabilitation were invited to complete an online questionnaire and semi-structured interview. Twenty-six people with stroke and 37 health professionals completed the questionnaire, while ten people with stroke and eight health professionals participated in an interview. People with stroke and health professionals who work with people with stroke

consider HIIT to be a beneficial intervention following stroke, however its use in clinical practice is varied based upon client motivation and clinician expertise. People with stroke reported minimal support from people with stroke and health professionals, the lack of knowledge of the benefits of HIIT, and the use of the term 'high intensity' as the main barriers to participation. Access to health professionals, the provision of personalised education and individualisation of the protocol were reported by people with stroke as the main facilitators to participation in HIIT. Health professionals reported a lack of knowledge about how to prescribe HIIT, and participant motivation as the main barriers to the prescription of HIIT within the clinical environment. Increased education about the prescription and benefits of HIIT, obtaining medical clearance for HIIT, and comprehensive screening prior to commencing a HIIT program were the main facilitators to HIIT prescription reported by health professionals working with people with stroke.

The third study investigated an alternative to BDNF, blood lactate, as a marker of brain plasticity given the challenges associated with measuring BDNF in clinical practice, such as cost, speciality training and equipment. Due to the Covid-19 pandemic recruiting people with stroke to participate in the study was not feasible, therefore, this study was completed in a healthy population of adults. Thirty-one healthy adults were tested for BDNF, and lactate concentrate before and after a submaximal graded exercise test. A poor correlation was observed between the two biomarkers at pre- ($r = -0.256$, $p = 0.164$) and post-exercise ($r = 0.112$, $p = 0.549$). The change in concentration from pre- to post-exercise ($r = 0.019$, $p = 0.921$) was also poorly correlated. Therefore, in healthy adults, there is little evidence to suggest a relationship between BDNF and lactate.

The fourth study examined the correlation between two upper limb assessment tools to identify paretic upper limb use within an Australian clinical setting. The Motor Activity Log Amount of Use (MALAOU) and the Motor Activity Log Quality of Movement (MALQOM) 30-item scales are commonly used in clinical practice. The Rating of Everyday Arm-use in the Community and Home (REACH) scale similarly measures paretic upper limb use but is much less time intensive compared to the MALAOU and MALQOM. Ten people with stroke completed MALAOU, MALQOM and REACH assessments before and after a two-week intensive upper limb program. A moderate correlation between the MALQOM and REACH

(rho = 0.717, p = 0.02) was observed at pre-intervention. No correlation was observed between any measure at any other timepoint, or when comparing the change in scores from pre- to post-intervention.

The fifth study included in this thesis is a protocol for a randomised controlled trial as a future research recommendation based upon the learnings of the other studies. The randomised controlled trial was originally planned to be completed during candidature, however due to the Covid-19 pandemic this was not feasible. This protocol, to be completed after this program of research, will explore the efficacy of a combined HIIT and Modified-CIMT upper limb function.

ACKNOWLEDGEMENTS

The rollercoaster that is a PhD has finally come to an end, and I wouldn't be where I am today with the support of numerous individuals along the way.

To my supervisors, Prof Suzanne Kuys, Dr Angelica Thompson-Butel and Dr Liam Johnson, I thank you for your expertise and guidance over the past three years. You have made me a more competent and confident researcher. I would also like to thank A/Prof Kate Hayward and Dr Simone Dorsch for your continued feedback and enthusiasm for this program of research. Thank you to Pamela, Kerrie, Matt, Steph, Sam, Laura, and Justine for your assistance within this project, you have enabled a higher quality of research. A big thank you to the research friends and mentors I have made through my studies; I greatly appreciate your guidance and the Zoom calls at odd hours due to time zones.

To my family and friends, thank you for being there for me every step. I would especially like to thank my mother and father, Sharon and Michael, and my sister Bec. You allowed me to pursue this goal, along with every other goal I have ever had, with endless support and unwavering love (I promise this is the last university degree). I cannot express the true influence you have had on my life, for which I will always be grateful. Thank you to my friends outside of the research world, you provided well needed escapes and distractions and cheered on my successes (even if you didn't really know what was going on).

To my grandmother and grandfather, Beverley, and Raymond, thank you for inspiring an amazing and very fulfilling career. Nan and Pop, I am sorry this research will not be able to help you directly, but I hope you are proud to be part of something that may allow other grandparents to be able to watch their grandchildren grow up.

To the people with stroke I had the honour of working with in my early days as an exercise physiologist, thank you. I thank you for sharing your stories, the good and the bad, which created the path for this research to hopefully allow all survivors to live the life they choose.

A final and very special thank you to the incredible participants who partook in this project, I am eternally grateful. Thank you for trusting me and creating memories I will never forget. I hope the experience was as enjoyable and rewarding for you as it was for me.

DECLARATION BY AUTHOR

This thesis contains no material that has been extracted in whole or in part from a thesis that I have submitted towards the award of any other degree or diploma in any other tertiary institution.
No other person's work has been used without due acknowledgment in the main text of the thesis.
All research procedures reported in the thesis received the approval of the relevant Ethics/Safety Committees (where required).

Name: Sarah Kate Ashcroft

Signature:

Date: 22/01/2024

TABLE OF CONTENTS

PUBLICATIONS WITHIN THIS THESIS

Ashcroft, S. K., Ironside, D. D., Johnson, L., Kuys, S. S., & Thompson-Butel, A. G. (2022). Effect of exercise on Brain-Derived Neurotrophic Factor in stroke survivors: A systematic review and meta-analysis. *Stroke*, *53*(12), 3706–3716. https://doi.org/10.1161/STROKEAHA.122.039919

CONTRIBUTIONS BY OTHERS TO THIS THESIS

A number of people, other than the PhD candidate and supervisory panel, contributed to the undertaking of the studies described in this thesis. Their names and contributions are listed below.

Contributor	**Statement of contribution**
Basclain, Kerrie	Analysis of samples to quantity BDNF concentration (Study 3, Chapter 7).
Chamberlain, Saran	Design of questionnaire and semi-structured interview questions (Study 2, Chapter 6).
Hoon, Matthew	Collection of blood samples (Study 3, Chapter 7).
Kempson, Clive	Design of questionnaire and semi-structured interview questions (Study 2, Chapter 6).
Living, Letisha	Design of questionnaire and semi-structured interview questions (Study 2, Chapter 6).
Polkinghorn, Terence	Design of questionnaire and semi-structured interview questions (Study 2, Chapter 6).
Starc, Laura	Assessment of participants (Study 3, Chapter, 7).
Steele, Michael	Statistics support (Study 1 and 3, Chapter 5 and 7).
Stynes, Justine	Design of semi-structured interview questions (Study 2, Chapter 6).
Walsh, Samantha	Assessment of participants (Study 3, Chapter 7).
Willis, Megan	Statistics support (Study 1, Chapter 5).
Woolnough, Catherine	Analysis of samples to identify BDNF genotype (Study 3, Chapter 7).

ABSTRACTS ARISING FROM THIS THESIS

Oral presentations

Ashcroft SK, Ironside DD, Johnson L, Kuys SS & Thompson-Butel, AG. The effect of aerobic exercise intensity and duration on Brain-Derived Neurotrophic Factor in stroke survivors: A systematic review and meta-analysis. August 2022. *Smart Strokes, Sydney, Australia*.

Poster presentations

Ashcroft SK, Johnson L, Kuys SS, Thompson-Butel AG. Is it all about timing? Effectiveness of aerobic exercise before or after upper-limb rehabilitation post-stroke: A protocol. October 2021. *Stroke Society of Australasia (SSA) Annual Scientific Meeting (ASM), Perth (Virtual), Western Australia, Australia*.

Ashcroft SK, Johnson L, Kuys SS, Thompson-Butel AG. High Intensity Interval Training (HIIT) following stroke: Perceptions of stroke survivors and health professionals. August 2022. *Stroke Society of Australasia (SSA) ASM, Christchurch, New Zealand*.

Ashcroft SK, Walsh SJ, Johnson L, Kuys SS, Thompson-Butel AG. High Intensity Interval Training POst-STroke (HIIT-POST): Preliminary results. August 2023. *Stroke, Melbourne, Australia*.

Other presentations

Ashcroft SK. Personalised Exercise for Priming and Prevention Post-stroke (PREPPP). April 2021. *Universities Australia Pitch It Clever*.

Ashcroft SK. Post-stroke: Giving survivors a hand. May 2021. *Australian Catholic University Pitch Plus (Winner)*.

Ashcroft SK. PeRsonalised Exercise for Priming Post-stroke (PREPP). September 2022. *Australian Catholic University 3 Minute Thesis*.

LIST OF ABBREVIATIONS AND SYMBOLS

ACSM	American College of Sports Medicine
ACU	Australian Catholic University
ADLs	Activities of Daily Living
BDNF	Brain-Derived Neurotrophic Factor
CIMT	Constraint-Induced Movement Therapy
ELISA	Enzyme-Linked Immunosorbent Assay
FITT	Frequency, Intensity, Time, Type
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
HIIT	High Intensity Interval Training
HR	Heart Rate
HREC	Human Research Ethics Committee
MAL	Motor Activity Log
MALAOU	Motor Activity Log Amount of Use Scale
MALQOM	Motor Activity Log Quality of Movement Scale
mBDNF	Mature Brain-Derived Neurotrophic Factor
MCID	Minimal Clinical Important Difference
mCIMT	Modified Constraint-Induced Movement Therapy
mRS	Modified Rankin Scale
ng/mL	Nanograms per millilitre
pg/mL	Picograms per millilitre
QoL	Quality of Life
RCT	Randomised Controlled Trial
REACH	Rating of Everyday Arm-Use in the Community and Home
rho	Spearman rank correlation coefficient
RPE	Rate of Perceived Exertion
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
SRRR	Stroke Recovery and Rehabilitation Roundtable
VO_2	Volume of oxygen uptake
WMFT	Wolf Motor Function Test

LIST OF TABLES

LIST OF FIGURES

KEYWORDS

Brain-Derived Neurotrophic Factor, high intensity aerobic exercise, lactate, neuroplasticity, rehabilitation, Stroke, upper limb.

Chapter 1 INTRODUCTION

This chapter introduces the thesis by presenting an overview of the areas of interest explored in this program of research and its significance to stroke rehabilitation practices.

1.1 General overview

Stroke is a broad term to describe a neurological deficit because of an acute injury to the central nervous system attributed to a vascular cause (Sacco et al., 2013). Stroke is the second leading cause of disability and mortality worldwide (Kuriakose & Xiao, 2020; MacLellan et al., 2011), and in Australia in 2020, more than 27,000 people experienced a stroke for the first time (Deloitte, 2020) and more than 475,000 Australians were living with the lasting effects of stroke (Stroke Foundation, 2020).

Most spontaneous functional recovery is achieved in the first few months' post-stroke (Grefkes & Fink, 2020) as a result of reperfusion and endogenous repair-related events that elicit neural protection (Cassidy & Cramer, 2017). To facilitate additional functional recovery, targeted rehabilitation interventions are required during stroke recovery (Cassidy & Cramer, 2017; Carmer, 2008). Rehabilitation interventions aim to optimise neuroplasticity, a process by which the brain adapts and modifies in structure and function (Alia et al., 2017; Cramer et al., 2011; Kiper et al., 2016; Voss et al., 2017) in response to stimulus of the nervous system (Cohen & Dimyan, 2011). Therefore, rehabilitation interventions aim to facilitate neurogenesis, neuroprotection, and functional gains (Wlodarczyk et al., 2021). The measurement of neuroplasticity within clinical practice may assist with the prediction of recovery and response to rehabilitation and may enable clinicians to personalise therapy to enhance CNS stimulation (Bernhardt et al., 2016; Kim & Winstein, 2017; Milot & Cramer, 2008). Brain-Derived Neurotrophic Factor (BDNF) is a biomarker considered to be a surrogate measure of neuroplasticity associated with neuronal development and survival (Balkaya & Cho, 2019; Huangl & Reichardt, 2001), energy metabolism (Knaepen et al., 2010; Marosi & Mattson, 2014) and functional prognosis post-stroke (Wlodarczyk et al., 2021). In both healthy and neurological populations, including stroke, high intensity aerobic exercise increases circulating BDNF concentrations (Mackay et al., 2017; Schmolesky et al., 2013). But to date, there is very

limited guidance for the exact exercise training parameters (i.e., frequency, intensity, time/duration, and type) required in a post-stroke cohort to produce increases in BDNF concentration which may facilitate increased neuroplasticity and functional improvement.

Identifying BDNF concentration may be useful to personalise post-stroke rehabilitation interventions within the clinical environment to individualise recovery (Boyd et al., 2017), however its measurement in clinical practice is not feasible due to cost and logistical challenges (Gonzalez et al., 2018). Lactate, a by-product of muscle glycolytic pathways during exercise (Skriver et al., 2014), is linked with synaptic plasticity, promoting the expression of neurotrophins such as BDNF (Wang, Xiang, Liu, et al., 2019) and can be cheaply and rapidly measured in clinical practice (Crotty et al., 2021), potentially making it a more feasible measure of neuroplasticity in the clinical environment. While increased BDNF (Mang et al., 2013) and lactate (Boyne et al., 2019) expression is demonstrated following high intensity aerobic exercise, few studies have explored the direct correlation between BDNF and lactate concentrations in healthy cohorts (Coco et al., 2013; Schiffer et al., 2011), and only one study has explored this relationship in stroke populations (Boyne et al. 2019). Further exploration of the relationship between these two biomarkers may enable clinicians to use lactate to individualise rehabilitation practices to facilitate neuroplastic and functional outcomes (Bernhardt et al., 2016; Kim & Winstein, 2017; Milot & Cramer, 2008).

High intensity aerobic exercise may be a 'primer' for motor skill training (Valkenborghs et al., 2019) due to its capacity to increase BDNF concentration, and brain neuroplasticity (Ploughman et al., 2015). High Intensity Interval Training (HIIT) is a safe and feasible intervention after stroke to improve mobility and gait outcomes, cardiovascular health, and neuroplasticity (Boyne et al., 2023; Crozier et al., 2018; Gjellesvik et al., 2021). Involving phases of high intensity activity and low intensity recovery periods (Gibala et al., 2012), numerous HIIT protocols have been explored in stroke literature (Boyne et al., 2023; Crozier et al., 2018; Gjellesvik et al., 2021; Valkenborghs et al., 2019). Though HIIT is yet to be incorporated into stroke clinical guidelines (Pin-Barre et al., 2021). Barriers to the uptake of physical activity and exercise following stroke have extensively been explored from the perspectives of people with stroke (Banks et al., 2012; Simpson et al., 2011) and health professionals who work with people with stroke (Moncion et al., 2020). However, few

studies have explored the specific experience of HIIT from the perspectives of people with stroke and health professionals working with people with stroke. Understanding the barriers, and facilitators, to HIIT after stroke may help improve the uptake and implementation of HIIT.

HIIT may also have a role to play in optimising motor skill rehabilitation. The use of high intensity aerobic exercise as a primer for motor skill acquisition has been explored across various populations, though it is unclear what the optimal prescription and timing of the exercise is for enhanced skill acquisition. Increased BDNF concentration, which may be facilitated by high intensity aerobic exercise, is associated with memory encoding and consolidation (van Dongen et al., 2016), and improved motor learning post-stroke (Quaney et al., 2009). When performed within close temporal proximity to skill training (i.e., within one hour), high intensity aerobic exercise may increase neuroplasticity (Thomas et al., 2017). There is evidence motor skill acquisition and retention may be improved by high intensity aerobic exercise performed before (Skriver et al., 2014; Valkenborghs et al., 2019) or after (Nepveu et al., 2017; Roig et al., 2012; Thomas et al., 2016) skill training. However, the optimal window of time (i.e., before or after motor skill training) in which the exercise should be performed by people with stroke to enhance the neuroplastic effects of skill training is unclear.

The increase in corticospinal excitability and general arousal have been posited as reasons for why HIIT after upper limb therapy may improve upper limb outcomes (Loras et al., 2020; Ostadan et al., 2016), enhance long-term memory (Roig et al., 2012) and motor skill retention post-stroke (Nepveu et al., 2017). However, this effect has only been demonstrated in a small sample size (n = 22) (Nepveu et al., 2017), therefore further exploration is required. Furthermore, the effect of fatiguing exercise performed before motor skill training should also be considered, particularly given fatigue is highly prevalent in people with stroke (Alghamdi et al., 2021) even without the addition of high intensity exercise training. A study exploring the feasibility and acceptability of high intensity aerobic exercise before and after upper limb therapy after stroke is needed.

1.2 Thesis overview

This thesis contains ten chapters to explore exercise prescription and uptake post-stroke by 1) identifying optimal exercise training parameters, 2) investigating barriers and facilitators to the prescription and uptake of exercise in clinical practice, and 3) examine the relationship between commonly used outcome measures of neuroplasticity and upper limb function (Figure 1-1). Chapters 1 and 2 provide an overview of this thesis. Chapter 3 outlines the implications of the Covid-19 pandemic on the conduct of this program of research. Chapter 4 outlines the various research methods used within this thesis. Chapters 5 to 7 comprise three original studies, respectively: 1) systematic review and meta-analysis to identify the exercise parameters needed to increase BDNF concentration post-stroke, 2) mixed methods study exploring the barriers and facilitators to HIIT after stroke, and 3) pre-post observation study to identify the relationship between BDNF and lactate concentration. Chapter 8 explores the relationship between two measures of upper limb function routinely used in clinical practice. Chapter 9 outlines a randomised controlled trial protocol designed to explore the effect of combined aerobic exercise and motor rehabilitation on upper limb skill acquisition. Finally, Chapter 10 summarises and discusses the key findings, as well as the clinical and research implications, of this research.

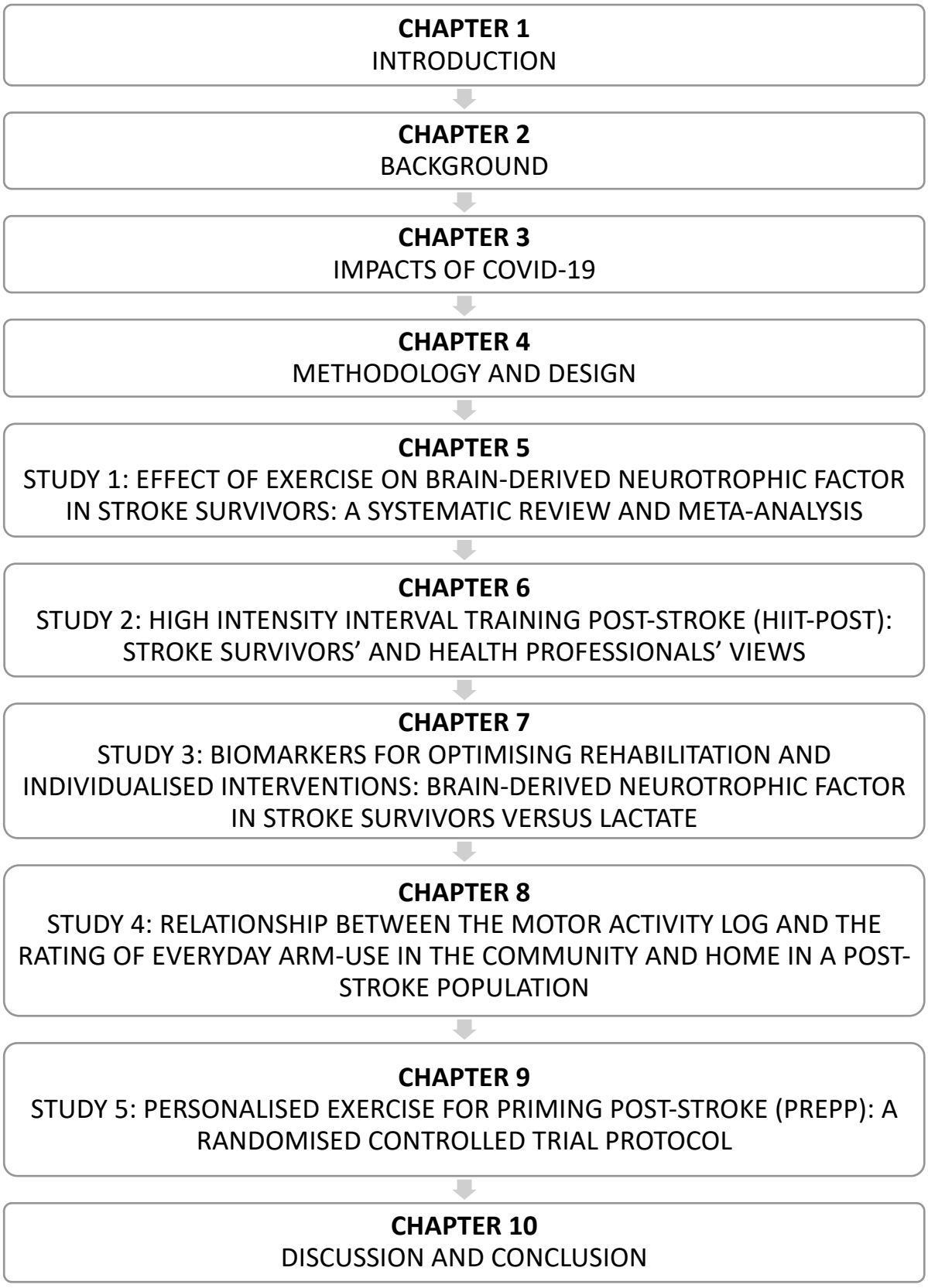


Figure 1-1 Thesis overview

Chapter 2 BACKGROUND

This chapter will provide a rationale for the research program by exploring the pathophysiology of stroke and the impact of neuroplasticity on post-stroke recovery. It will also provide insight into the association between exercise and neuroplasticity, as well as the measurement of neuroplasticity from a clinical practice perspective. Finally, this chapter will discuss the role of exercise in stroke recovery, exploring the current recommendation and potential limitations to the implementation of guidelines in real-world practice.

2.1 Stroke

2.1.1 Stroke aetiology

Stroke is characterised as a neurological deficit caused by an acute focal injury of the central nervous system attributed to a vascular cause, persisting for ≥24 hours or until death (Sacco et al., 2013). The disturbance of function within the brain has resulted in the description of stroke as a destructive cerebrovascular disease (Liu et al., 2020). Stroke can be classified as ischaemic or haemorrhagic, characterised by the mechanism of disturbance to cerebral vessel function. Ischaemic stroke occurs as a result of an occlusion (Grysiewicz et al., 2008) or clot within a cerebral vessel which limits blood, oxygen, and nutrient flow to a region of the brain (Liu et al., 2020). Common causes of ischaemic stroke include large vessel artery atherosclerosis, cardiogenic embolism, and small vessel occlusive disease (Kim et al., 2015). Haemorrhagic stroke occurs as a result of a rupture of a cerebral vessel (Grysiewicz et al., 2008). Haemorrhagic stroke is further stratified according to the location of the brain region in which the damage is contained (e.g., intracerebral haemorrhage in which the bleed is contained within the brain) (Grysiewicz et al., 2008). A third classification of cerebral disease is a Transient Ischaemic Attack (TIA). A TIA is characterised by an acute loss of focal cerebral function (Pendlebury et al., 2009), where symptoms typically spontaneously resolve within an hour of onset (Amarenco, 2020). New evidence has suggested a TIA is a 'tissue-based' event, with no ischaemic lesion visible on brain imaging, which differs from ischaemic or haemorrhagic stroke (Amarenco, 2020).

2.1.2 Stroke epidemiology

2.1.2.1 Distribution of stroke

Stroke is the second leading cause of disability and mortality worldwide (Kuriakose & Xiao, 2020) and is the second-most common cause of disability-adjusted life years (Saunders et al., 2016). Stroke is attributed to 44 million disability-adjusted life years per year (Deloitte, 2020). In Australia alone, more than 475,000 individuals are currently living with the lasting effects of stroke (Stroke Foundation, 2020), which include mental and bodily function disability (Pollock et al., 2014), reduced independence (Camak, 2015) and financial burden (Katan & Luft, 2018).

Early deaths (<30 days) post-stroke account for approximately 28% of stroke mortality (Bronnum-Hansen et al., 2001), with many attributed to brain injury, secondary complication (e.g., pneumonia, sepsis, pulmonary embolism), or cardiac disease after the event (Singh et al., 2018). The five-year mortality rate of stroke may be as high as 40 to 60% (Corraini et al., 2018), with higher rates of mortality associated with haemorrhagic stroke (Koton et al., 2014; Schmidt et al., 2014). A large proportion of people with stroke die of further cardiovascular disease (e.g., ischaemic heart disease or secondary stroke) and cancers, likely due to the overlap of risk factors associated with stroke and these diseases (Rutten-Jacobs et al., 2015; Stark et al., 2021).

2.1.2.2 Determinants of stroke

The risk factors associated with stroke show some variation depending on the specific classification of the stroke in question. Increased age, sex (male), hypertension, diabetes mellitus and lifestyle factors such as smoking, physical inactivity, and alcohol consumption are risk factors for ischaemic and haemorrhagic stroke (Ahangar et al., 2018; Boehme et al., 2017; Grysiewicz et al., 2008). The cumulative risk of secondary stroke is approximately 26.4% at five-years and 39.2% at ten-years post-initial stroke (Singh et al., 2018). Additional risk factors for ischaemic stroke include race (i.e., Black, and Hispanic (Grysiewcz et al., 2008), and Indigenous populations (Dos Santos et al., 2021)), family history of stroke, atrial fibrillation (Grysiewicz et al., 2008), and dyslipidaemia (Ahangar et al., 2018; Ploughman & Kelly, 2016). Additional risk factors for haemorrhagic stroke include race (i.e., Asian or

African American populations) (Grysiewicz et al., 2008) and opioid addiction (Ahangar et al., 2018).

While stroke is typically more prevalent in 'older persons' (i.e., 65+ years), there is an increasing incidence of stroke in younger populations. More instances of stroke among Australians aged between 20 to 54 years are being recorded than previously (Boehme et al., 2017; Doyle et al., 2014; Putaala, 2016). This shift in age profile of people experiencing a stroke may be attributed to an increased prevalence of lifestyle risk factors (e.g., alcohol consumption, illicit drug use, physical inactivity, obesity) as well as changes in modern life (e.g., long working hours, chronic stress, sleep deprivation) (Putaala, 2016). Physical inactivity is one of the five risk factors associated with more than 80% of all stroke cases, and approximately 29% of population-attributable risk for ischaemic and haemorrhagic stroke (O'Donnell et al., 2010). Physical inactivity is also a modifiable risk factor with demonstrated links to other stroke risk factors including hypertension, metabolic conditions, and poor body composition (Boehme et al., 2017; Guzik & Bushnell, 2017). Physical activity improves heart and circulatory function, increases the concentration of beneficial lipoproteins, and reduces the concentration of clotting molecules (Gallanagh et al., 2011). Increasing moderate intensity physical activity may reduce the risk of stroke by a minimum of 15%, with more hours of physical activity associated with greater reductions in stroke risk (Gallanagh et al., 2011). Targeted interventions to increase levels of physical activity may be beneficial to reduce the global burden of stroke (O'Donnell et al., 2010) and risk of secondary stroke (Gallanagh et al., 2011). This research program will explore the use of exercise (a structured form of physical activity) to optimise stroke recovery. Understanding the classification, distribution, and determinants of stroke is necessary to allow the development of targeted rehabilitation interventions.

2.1.3 Impairments after stroke

A myriad of potential post-stroke impairments exist, dependent upon the severity of cerebral damage (Shiner et al., 2016), the brain region affected (Berretta et al., 2014), and pre-stroke comorbidities (Sewell et al., 2021). Cerebral damage, identified using Magnetic Resonance Imaging (MRI), is reported on a spectrum, ranging from minimal to significant corticospinal tract damage which is associated with more significant impairment (Quinlan et

al., 2015). Impairment is also associated with the location of the cerebral damage, where the function of the brain in that region is impaired resulting in functional deficits (Saunders et al., 2016). The presence of comorbidities, typically cardiovascular or metabolic in nature, may also be attributed to increased impairment, reduced function, and subsequent reductions in independence (Sewell et al., 2021). Reductions in function may also be linked to reduced levels of physical activity (Viktorisson et al., 2021). Impairments post-stroke may reduce movement, cognition, and mood dependent on the region of the brain.

2.1.3.1 Motor impairments

Motor impairments are experienced by approximately 80% of people with stroke, typically affecting the movement of the face, upper and/or lower limb, on the contralateral side of the affected brain region (Birchenall et al., 2019; Molle Da Costa et al., 2019; Tomita et al., 2019). Post-stroke motor impairments are the result of decreased descending neural input to alpha motor neurons, resulting in the degeneration of downstream muscle fibres (Gray et al., 2012). This damage reduces the number (Beckwée et al., 2021) and firing rate (McNulty et al., 2014) of skeletal muscle motor units activated when the neural input arrives at the muscle, in particular type II fibres, eliciting a shift towards the activation of larger and slower motor units to facilitate movement (Gray et al., 2012). Motor impairments are associated with limb dysfunction (Charalambous et al., 2018; Valkenborghs et al., 2019), contributing to diminished functional ability (Chaturvedi et al., 2020) and reduced mobility (Koroleva et al., 2020). Such dysfunction includes difficulty completing activities of daily living (ADLs) and pre-stroke activities, limiting participation (Koroleva et al., 2020). Motor impairments may have negative implications for ADLs and quality of life (QoL) post-stroke (Birchenall et al., 2019). For example, motor impairments of the upper limb may interfere with self-care activities (e.g., grooming, feeding) (Pollock et al., 2014; Yamamoto et al., 2020) resulting in reduced functional independence and QoL post-stroke (Kelly et al., 2018; Taub et al., 2006). Common motor impairments observed post-stroke include muscle weakness (Hunnicutt & Gregory, 2017), spasticity (Shiner et al., 2020), contractures (Matozinho et al., 2021), reduced inter-joint coordination (Mandehgary Najafabadi et al., 2019; Tomita et al., 2017) and reduced manual dexterity (Birchenall et al., 2019).

People with stroke also experience reductions in cardiorespiratory fitness. Fitness levels vary among people with stroke, however, most people with stroke achieve a peak oxygen consumption during exercise testing (VO_{2peak}) of approximately 8 to 15mL.kg^{-1}.min^{-1}, which is approximately 40 to 50% of age- and sex-matched populations (Ploughman & Kelly, 2016). People with stroke also expend more energy during ADLs, for example, people with stroke expend more energy walking at equivalent speeds compared to their healthy counterparts (Kramer et al., 2016; Ploughman & Kelly, 2016). A relationship exists between chronic physical inactivity, reduced cardiorespiratory fitness (Saunders et al., 2016), muscle weakness, and the loss of independence and activity engagement (de Morais et al., 2018).

2.1.3.2 Upper limb impairments after stroke

'Upper limb impairment' is an umbrella term for the reduced sensorimotor function of the arm, hand, and fingers of an individual (Pollock et al., 2014). Common upper limb impairments include paresis (Hunnicutt & Gregory, 2017), spasticity (Bakheit et al., 2010; Cusick et al., 2015), contractures (Matozinho et al., 2021), reduced inter-joint coordination (Mandehgary Najafabadi et al., 2019; Tomita et al., 2017), reduced manual dexterity (Birchenall et al., 2019; Kong et al., 2011), altered somatosensation (Carey, 1995; Yilmazer et al., 2019), and reduced proprioception (Carey, 1995; Rinderknecht et al., 2018). Contralateral hemiparesis is the predominant upper limb motor deficit (Hatem et al., 2016), evident among approximately 50 to 80% of people with stroke during the acute phase of recovery (i.e., one to seven days), which persists into the chronic phase (i.e., ≥6 months) of stroke recovery for 40 to 50% of people with stroke (Hussain et al., 2021).

Impairments of the upper limb are often persistent and disabling (Pollock et al., 2014). Deficits in upper limb motor and/or somatosensory function can increase the difficulty of performing ADLs, such as bathing, grooming, and feeding, and often leads to learned non-use of the paretic arm (Bakhti et al., 2017; Molle Da Costa et al., 2019). '*Learned non-use'* of the paretic arm is a behavioural phenomenon arising following numerous unsuccessful attempts to use the paretic extremity, as well as the positive reinforcement of compensatory strategies to complete tasks (Molle Da Costa et al., 2019). As a result, people with stroke may avoid the use of their paretic upper limb when completing ADLs (Bakhti et al., 2017; Molle Da Costa et al., 2019) and compensate by excessive use of the non-paretic

upper limb (Bakhti et al., 2017). Upper limb impairment, and learned non-use, of the paretic limb may result in increased anxiety, poor health-related QoL, and negative subjective wellbeing (Pollock et al., 2014). It has also suggested that upper limb dysfunction may be associated with low self-esteem and reduced motivation to engage in rehabilitation (Lieshout et al., 2020). A strong association exists between upper limb use, QoL, and functional independence (Kelly et al., 2018; Taub et al., 2006). Increased use of the paretic upper limb as a result of upper limb rehabilitation is associated with improvements in mood and sense of self (Lieshout et al., 2020). These in turn improve QoL as people with stroke experience increased autonomy and engagement in daily activities (Kelly et al., 2018).

2.2 Trajectory of stroke recovery

Stroke recovery can be a multifaceted process described using a temporal framework which outlines critical timepoints and the biological markers of each stage (Bernhardt et al., 2017). The use of a standardised recovery framework (Figure 2-1) may assist in the development of appropriate rehabilitation interventions, according to the underlying mechanisms of recovery at each stage, to optimise the facilitation of functional benefits throughout recovery (Bernhardt et al., 2017).

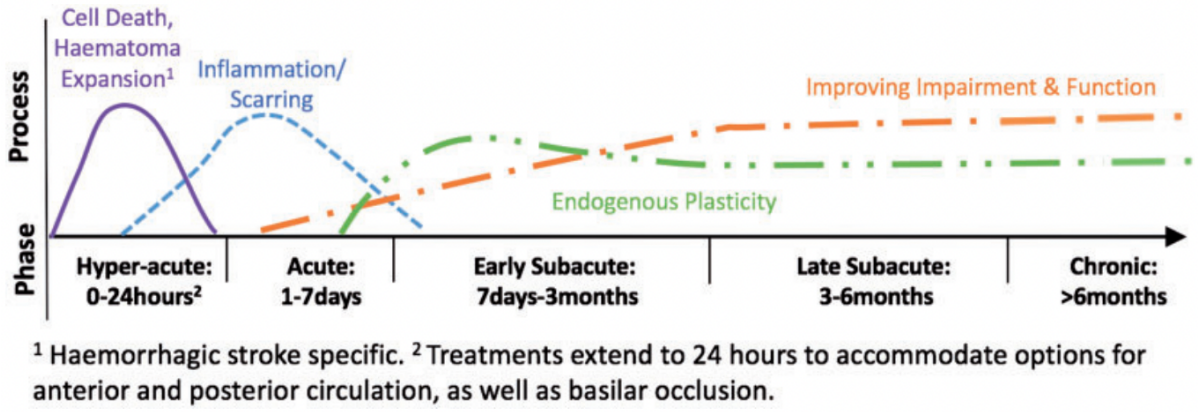


Figure 2-1 Framework of stroke recovery timepoints and underlying mechanisms (Bernhardt et al., 2017)

As seen in Figure 2-1, post-stroke recovery can be divided into five timepoints; hyper-acute, acute, early subacute, late subacute, and chronic (Bernhardt et al., 2017). Different biological mechanisms underpin recovery at different timepoints post-stroke. Within the initial hours post-stroke (hyper-acute and acute phases), reperfusion, or neuroprotection

occur in an attempt to salvage threatened tissue (Cassidy & Cramer, 2017). Within days to weeks post-event (early and late subacute phases), the initiation of brain repair occurs (Carey et al., 2002; Cassidy & Cramer, 2017). In the chronic phase of recovery, the brain is relatively stable, however modification of brain function and structure is still possible (Cassidy & Cramer, 2017). A clear understanding of the underlying mechanisms of recovery post-stroke is necessary to optimise rehabilitation.

2.2.1 Spontaneous recovery after stroke

The disturbance of cerebral function attributed to stroke causes an array of neurological injuries, including substantial tissue damage and subsequent disruption of the neural communication pathways responsible for function (Wieloch & Nikolich, 2006). However, stroke also triggers a cascade of cellular and molecular processes which facilitate neural protection and 'spontaneous recovery' (Cassidy & Cramer, 2017; Overman & Carmichael, 2014).

Spontaneous recovery is the improvement of behavioural function with limited targeted rehabilitation, that begins to occur after stroke within a heightened window early after stroke (Bernhardt et al., 2017). The window of time in which spontaneous biological recovery occurs varies in duration dependent on the neural system in question (Bernhardt et al., 2017), but rarely is full recovery achieved during this period of time (Cassidy & Cramer, 2017). Spontaneous recovery is proposed to be attributable to axonal repair, neurogenesis, and the resolution of inflammation following stroke (Yu, Washington & Kernie, 2014). While most spontaneous recovery and subsequent functional gains are evident in the first three months post-stroke (Grefkes & Fink, 2020), improvements in other systems affected by stroke (e.g., visuospatial, cognition, language) may take longer (Cassidy & Cramer, 2017; Pedersen et al., 1998). Most spontaneous recovery is classified as compensation, whereby brain regions away from the injured area assume the function of the injured area (Cassidy & Cramer, 2017; Cramer et al., 2011; Johansen-Berg et al., 2002). Simultaneously, diaschisis (reduced activity in connecting brain regions remote from the lesion site (Enager, Gold & Lauritzen, 2004)) occurs as a result of the interruption of neural connections between the area of cerebral damage and remote areas of the brain due to partial disruption of the neurovascular coupling (altered perfusion due to altered neural

activity) (Carrera & Tononi, 2014; De Silva & Faraci, 2017). Consequently, diaschisis can result in the functional decline in areas of the brain not near the injured region such as reductions in cerebral blood flow, metabolism, and neurotransmitters (Carmichael et al., 2004; Cassidy & Cramer, 2017; Kim, Lim & Park, 2019). To optimise stroke recovery, interventions after the window of spontaneous recover are needed to promote further neural recovery and may be considered useful post-stroke.

Neural structure and function

The recovery of neural activity temporarily diminished as a result of the stroke, is associated with functional motor recovery (Cramer et al., 2011; Schaechter et al., 2006). Increased excitability of the ipsilesional hemisphere (same side as the injury) is associated with motor recovery (Cassidy & Cramer, 2017; Johansen-Berg et al., 2002), evident by improved performance of ADLs between five- and 30-days post-stroke (Manganotti et al., 2002). The contralesional hemisphere (opposite side of injury) may also play a role in motor function recovery (Johansen-Berg, 2007). Recruitment of the contralesional hemisphere may occur due to hyperexcitability in the contralateral motor cortex after stroke (Buetefisch, 2015; Dodd, Nair & Prabhakaran, 2017). It is proposed that an interhemispheric imbalance is evident after stroke, whereby the ipsilesional hemisphere does not inhibit the contralesional hemisphere, and the contralesional hemisphere inhibits the ipsilesional hemisphere (Dodd, Nair & Prabhakaran, 2017). Thus, the degree of hemispheretic imbalance is correlated with the degree of motor impairment (Dodd, Nair & Prabhakaran, 2017). Contralesional hemisphere activation may produce increased movement yet with poor performance of fine motor tasks (Calautti et al., 2007). Progressive reductions in contralesional hemisphere recruitment and greater increases in ipsilesional recruitment via motor rehabilitation (Quinlan et al., 2015) can facilitate greater functional outcomes (Cassidy & Cramer, 2017).

Reorganisation, or remapping, of somatotopic representation also occurs as a result of spontaneous neural recovery post-stroke (Cassidy & Cramer, 2017; Cramer & Crafton, 2006). Brain imaging studies post-stroke illustrate wide cortical areas are recruited during motor function (Johansen-Berg, 2007), and are often termed ‘remapping’ (Cassidy & Cramer, 2017) ((Figure 2-2) (Johansen-Berg, 2007) and Figure 2-3 (Cramer, 2008)) or ‘reorganisation’ (Grefkes & Ward, 2014). The extent of cortical remapping is associated with

the size of the lesion, location of the lesion and subsequent rehabilitative practices (Cassidy & Cramer, 2017; Grefkes & Ward, 2014). The release of neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF) and Vascular Endothelial Growth Factor may also facilitate the reorganisation of cortical mapping by promoting synaptogenesis and dendritic spine formation and ramification (Alcantara et al., 2018). Further studies suggest that there may be an initial overactivation of sensorimotor cortical areas which decreases as recovery progresses, suggesting that the renormalisation of neural activity underlies motor function recovery (Ward et al., 2003).

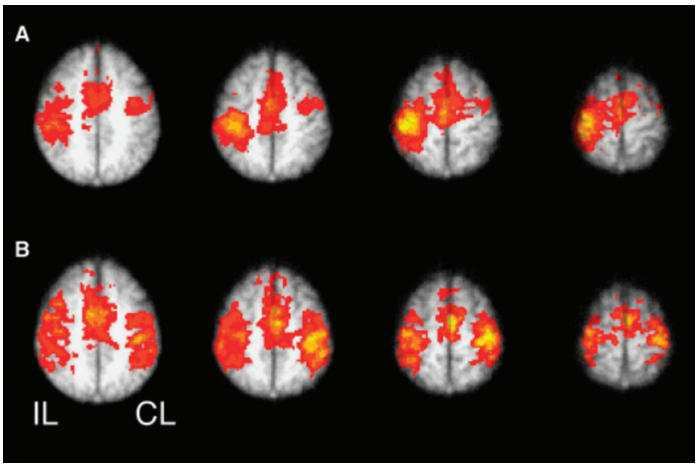


Figure 2-2 Pattern of brain activity during finger tapping of (A) non-paretic and (B) paretic upper limb. IL: ipsilesional hemisphere; CL: contralesional hemisphere (Johansen-Berg, 2017)

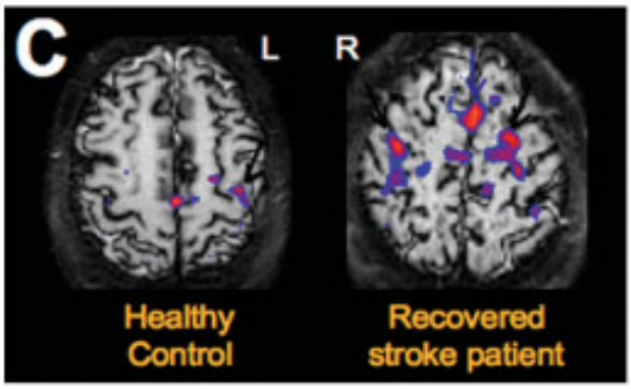


Figure 2-3 Neural activation is more bilateral during paretic finger tapping post-stroke, whereas it is more contralateral in healthy populations (Cramer, 2008)

A biomarker refers to an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions that can be objectively measured and

evaluated (Atkinson et al., 2001). Measurement of biomarkers of brain function could be used to monitor long-term outcomes after stroke, as recommended by the Stroke Recovery and Rehabilitation Roundtable (SRRR; Boyd et al., 2017). Functional Magnetic Resonance Imaging or Transcranial Magnetic Stimulation are two biomarkers recommended by the SRRR (Boyd et al., 2017), however these imaging methods provide numerous challenges. fMRI results may exhibit substantial variability due to various endogenous and exogenous factors that are difficult to control (Spetch, 2020). Functional tasks to be completed by the person with stroke during Functional Magnetic Resonance Imaging must be designed in accordance with functional impairments, which may prove difficult after stroke (Veldsman, Cumming & Brodtmann, 2015). For example, Johansen-Berg (2007) and Cramer (2008) conducted Functional Magnetic Resonance Imaging during finger tapping, therefore some finger function was required for this assessment. Transcranial Magnetic Stimulation may not be effective in acute stroke, and questions have been raised regarding equal efficacy of results between the upper and lower limbs (Xu & Sun, 2020). In addition, Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation are costly, requiring expensive equipment and ongoing staff training to facilitate its use (Connell et al., 2018; Crofts, Kelly & Gibson, 2020). Therefore, this program of research will explore alternative biomarkers that do not require a minimal level of motor function to complete the assessment and can be used across the spectrum of stroke recovery.

2.2.2 Motor learning effects on the brain

Spontaneous behavioural recovery often plateaus within three-months after stroke, and reach its limit at six-months (Grefkes & Fink, 2020). In the chronic phase of recovery (i.e., more than six-months post-stroke), brain repair slows to the stabilising of endogenous repair-related events (Cassidy & Cramer, 2017; Wahl & Schwab, 2014). However, further modifications in brain structure and functional improvements are possible via targeted rehabilitative interventions (Cassidy & Cramer, 2017; Cramer, 2008; Wahl & Schwab, 2014). Motor rehabilitation optimises neuroplasticity within the brain (Cramer et al., 2011), which refers to the brain's ability to adapt and modify in structure and function in response to a stimulus (Alia et al., 2017; Cramer et al., 2011; Kiper et al., 2016; Voss et al., 2017). Neuroplasticity is associated with neurodevelopmental and protection processes, such as synaptogenesis, neurogenesis, and neuroprotection (Wlodarczyk et al., 2021) which can

occur in response to rehabilitation (Cramer et al., 2011). Personalised rehabilitation can elicit increases in domain-specific and functional changes specific to the individual and phase of stroke recovery (Cassidy & Cramer, 2017; Wahl & Schwab, 2014).

Biomarkers as an indicator of motor learning

Biomarkers can be used as surrogate measures of disease state that can assist with the prediction of recovery and treatment response (Bernhardt et al., 2016; Kim & Winstein, 2017; Milot & Cramer, 2008). Biomarkers such as Matrix Metalloproteinase, BDNF, Vascular Endothelial Growth Factor and Angiopoietin 2 (Wlodarczyk et al., 2021) include genetic factors that are associated with the underlying processes of stroke recovery in the neurological deficit, functional ability, and social participation domains post-stroke (Lindgren & Maguire, 2016). Therefore, the measurement of biomarkers predictive of stroke recovery may provide an insight into the potential effectiveness of rehabilitation interventions in stroke (Cassidy & Cramer, 2017; Milot & Cramer, 2008; Wlodarczyk et al., 2021). Increases in BDNF concentration are associated with increased neuroplasticity in the post-stroke brain following rehabilitation (Ploughman et al., 2015) potentially due to synapse strengthening and axonal sprouting (Sawaki et al., 2008). BDNF is also associated with the processes of memory formation (van Dongen et al., 2016) and motor learning post-stroke which may promote recovery (Ploughman et al., 2009). This program of research will endeavour to better understand the connections between BDNF, aerobic exercise, and therapy-induced neuroplasticity.

Skill acquisition, consolidation, and retention

Motor learning requires repetitive task practice and the consolidation of an elaborated memory trace; therefore rehabilitation must target one or both of these processes (Debarnot et al., 2019). During repetitive task practice, motor skill acquisition is achieved. During this process, motor skill sequencing is achieved quickly with marked improvement in performance (Dahms et al., 2020). Therefore, motor skill acquisition involves improved encoding of the movement (Dahms et al., 2020; Hikosaka et al., 2002). Following acquisition, the learned motor sequence is stabilised to consolidate the skill (Dahms et al., 2020). Consolidation of the motor sequence provides increased resistance to interference, reducing the need for error correction during execution of the skill (Dahms et al., 2020). The

final stage of motor skill development is the retention of the learnt sequence (Dahms et al., 2020). During the retention phase, movement execution becomes more automatic and the motor map for the movement is robust (Dahms et al., 2020). BDNF is associated with encoding (i.e., acquisition phase) and consolidation phases (van Dongen et al., 2016).

2.2.2.1 Influence of exercise on motor learning

Aerobic exercise has been demonstrated to improve motor learning (Quaney et al., 2009), memory formation, and memory retention within apparently healthy (Roig et al., 2016) and stroke populations (Nepveu et al., 2017). Results from three systematic reviews demonstrate improvements in motor learning following aerobic exercise interventions (Roig et al., 2013; Roig et al., 2016; van Uffelen et al., 2008). However, the aerobic exercise prescription and its temporal proximity to motor skill training are variable within these studies, reflecting the limited understanding of how aerobic exercise may facilitate motor learning. It is also unclear how factors such as personal characteristics, the type of skill and memory in question, and the exercise training principles utilised (Figure 2-4) (Roig et al., 2016) influence motor learning.

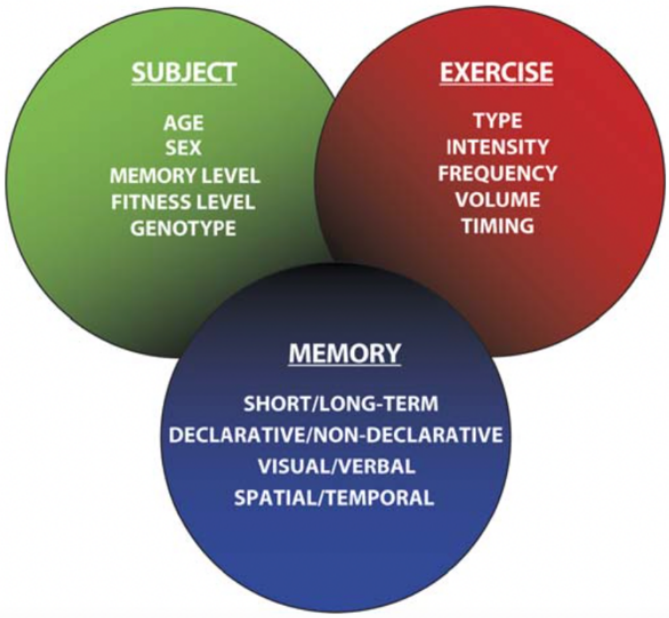


Figure 2-4 Factors that may modulate the effects of aerobic exercise on memory (Roig et al., 2016)

To better understand the relationship between BDNF, aerobic exercise and neuroplasticity post-stroke, this research includes a study protocol to explore the relationship between the timing of an aerobic exercise intervention and upper limb motor skill acquisition.

2.3 Brain-Derived Neurotrophic Factor

BDNF is produced and secreted within the central and peripheral nervous systems, platelets, vascular endothelial, smooth muscle cells, various immune cells, and skeletal muscle fibres (Yilmazer et al., 2019). It is proposed that three-quarters of an individual's BDNF concentration originates from brain tissue (Rasmussen et al., 2009). The processes by which BDNF is produced are illustrated in Figure 2-5. BDNF messenger ribonucleic acid (mRNA) is translated into precursor BDNF in the endoplasmic reticulum (Balkaya & Cho, 2019), which is then transported into the Golgi apparatus and processed into mature BDNF (mBDNF) by extracellular protein convertase 1 (PC1) within the vesicles (Marosi & Mattson, 2014). mBDNF can also be formed extracellularly by tissue-type plasminogen (tPA) which activates plasminogen, following which the precursor molecule is cleaved (Marosi & Mattson, 2014). Alternatively, extracellular metalloproteinases can process precursor BDNF to generate mBDNF in the extracellular space (Balkaya & Cho, 2019; Marosi & Mattson, 2014).

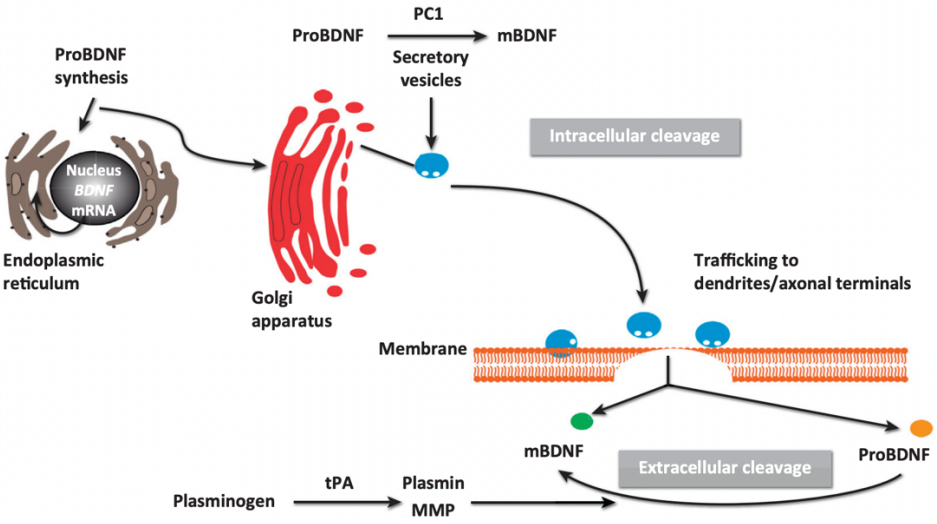


Figure 2-5 Mechanisms of the production and release of BDNF (Marosi & Mattson, 2014)

BDNF is closely linked to the processes of energy metabolism and maintenance of homeostasis within the central and peripheral nervous systems (Knaepen et al., 2010;

Marosi & Mattson, 2014). BDNF can attenuate neuronal injury and repair brain damage (Liu et al., 2020) through its function in promoting growth and survival of neurons (Binder & Scharfman, 2004). Due to the widespread nature of BDNF within the body, BDNF is considered a mediator of adaptive responses of the brain and body in response to energy intake and expenditure (Marosi & Mattson, 2014). The main functions of BDNF include neuron protection and survival, neurite (neuronal projection) expression, axonal and dendrite growth and remodelling, neuronal differentiation (maturation), as well as synaptic plasticity (Alcantara et al., 2018; De Vincenti et al., 2019; Knaepen et al., 2010). The capacity of BDNF to facilitate neurogenesis (Alcantara et al., 2018), strengthen excitatory synapses and weaken inhibitory synapses (Binder & Scharfman, 2004) is pivotal to its role in neuroplasticity (Alcantara et al., 2018).

The release of BDNF may be mediated and controlled by external factors. BDNF is secreted in an activity-dependent manner (Knaepen et al., 2010) from both neurons and axons in response to neuronal activity and binds to tropomyosin-related kinase receptors (Balkaya & Cho, 2019). Through its affinity with tropomyosin receptor kinase B (Ibrahim et al., 2022), BDNF can influence neuro-morphological development and synaptic activity (Cassidy & Cramer, 2017). BDNF levels may be increased following the learning of complex motor skills (Cassidy & Cramer, 2017; Marosi & Mattson, 2014), or the completion of exercise (Knaepen et al., 2010; MacLellan et al., 2011). Exercise is proposed to increase BDNF transcription within the brain, with increased secretion from cerebral vascular endothelium (Rasmussen et al., 2009). It is also proposed that BDNF is produced within the skeletal muscle bed in response to muscle contraction during exercise (Matthews et al., 2009). The change in BDNF concentration post-exercise has been examined following various exercise interventions in both apparently healthy and post-stroke populations. The effect of exercise on BDNF concentration may vary according to the modality of exercise. In a healthy population, acute aerobic exercise can increase circulating BDNF concentration by up to 20 to 40% (Schmolesky et al., 2013; Yarrow et al., 2010), while overloaded resistance training can increase circulating BDNF by 32% (Yarrow et al., 2010). In a stroke population, a single session, or program (20.6 ± 20 hours), of aerobic exercise can significantly increase BDNF concentration (Mackay et al., 2017). However, the effects of traditional resistance exercise

on BDNF concentration in a stroke population has not been explicitly explored in systematic evidence.

2.3.1 BDNF after stroke

Immediately post-stroke BDNF concentration is transiently reduced with larger infarcts causing greater reductions (Qiao et al., 2017). In the immediate aftermath of a stroke, serum BDNF is reduced (Algin et al., 2019), before being observed to rise in brain tissue surrounding the region of damage (Berretta et al., 2014) during the acute and sub-acute stage of stroke recovery.

Low BDNF concentration is associated with poorer long-term functional and cognitive outcomes (Pedard et al., 2018; Wlodarczyk et al., 2021), still evident at 2- and 7-years following stroke (Stanne et al., 2016). A negative correlation has been found between serum BDNF concentration and modified Rankin Scale (mRS) score, with poor functional outcomes (mRS score of 3-6, where 6 represents death) associated with lower BDNF concentration (Stanne et al., 2016; Wang et al., 2017). Therefore, BDNF might be considered an independent predictor of poor functional status (Wang et al., 2017), though the range of BDNF concentration associated with positive outcomes post-stroke remains unclear (Luo et al., 2019; Stanne et al., 2016; Wlodarczyk et al., 2021).

The role of BDNF in the promotion of neuronal growth, proliferation and neuroplasticity suggests it has potential application in post-stroke rehabilitative therapy (Balkaya & Cho, 2019; Bang, 2017). Levels of neurogenesis are commonly utilised as an indirect assessment of the effectiveness of rehabilitation during stroke recovery (Liu et al., 2020), and higher levels of BDNF are associated with neurogenesis and enhanced neuroplasticity. Studies have demonstrated BDNF is a crucial mediator of motor learning, facilitated through post-stroke rehabilitation (Ploughman et al., 2009). Peripheral BDNF concentration and motor function recovery rate have been shown to be positively correlated (Ploughman et al., 2009; Sun et al., 2014). Utilising interventions that increase BDNF may assist in enhancing motor performance (Hariri et al., 2003), but further exploration into the effect of exercise on BDNF concentration post-stroke is needed.

2.3.2 Impact of interpersonal differences on BDNF

Natural variation in basal (resting) BDNF concentrations are expected due to an array of contributing factors (Mackay et al., 2017). While no large-scale studies have explored potential confounders of BDNF concentration, positive correlations have been identified with increased exposure to sunlight (e.g., summer) (Molendijk et al., 2012) and the luteal phase of the menstrual cycle (Begliuomini et al., 2007). Alternatively, an inverse correlation has been proposed between BDNF concentration and body mass index (BMI) (Alomari et al., 2020; Lommatzsch et al., 2005; Taha et al., 2023). However, it is unclear if these variables consistently affect BDNF concentration.

2.3.2.1 BDNF polymorphism

The genomic variant within a single position of deoxyribonucleic acid (DNA) is called a 'single nucleotide polymorphism (SNP)'. An SNP occurs when a particular nucleotide is replaced by an alternative one (Berretta et al., 2014; Cassidy & Cramer, 2017). Numerous potential SNP variations exist within BDNF, including rs6265 (Val66Met) or G189A, rs10767664, rs10501087 or rs988712 (Balkaya & Cho, 2019). The Val66Met polymorphism is the most common BDNF genetic polymorphism, which occurs because of the substitution of a valine (Val) with a methionine (Met) at codon 66 of the BDNF gene (Balkaya & Cho, 2019). This substitution alters the structure of BDNF (Anastasia et al., 2013), resulting in abnormal intracellular trafficking (i.e., abnormal packaging of precursor BDNF) and reducing the concentration of mBDNF secreted (Egan et al., 2003; Hariri et al., 2003). The altered concentration of mBDNF results in limited activity-dependent section of BDNF (Balkaya & Cho, 2019; Canivet et al., 2015; Egan et al., 2003) and reduced BDNF neurotrophic support (Lemos et al., 2016), attributed to improper protein folding and impaired molecular processing (Chen et al., 2004; Egan et al., 2003; Lemos et al., 2016). The Val66Met polymorphism is also attributed to reduced BDNF production in the central nervous system and subsequent reductions in circulating BDNF concentrations (Knaepen et al., 2010; Lemos et al., 2016; Ozan et al., 2009). These structural and function changes are associated with the reduction in BDNF concentration increase typically observed following exercise, however the exact effects are disputed within the literature (Helm et al., 2017; Lemos et al., 2016).

2.3.2.2 Impact of BDNF polymorphism on stroke recovery

The presence of the Val66Met SNP is associated with significantly greater cerebral atrophy (Cramer et al., 2022), but does not eliminate the ability to recover after stroke (French et al., 2018; Di Pino et al., 2016). This is linked to the proposal that people with stroke with the Val66met polymorphism require enhanced subcortical plasticity to facilitate greater recovery (Di Pino et al., 2016). People with stroke with the Val66Met polymorphism demonstrate approximately 3.4-fold reductions in brain activation during paretic limb movement when compared to people with stroke without this polymorphism (Kim, Quinlan, Gramer, et al., 2016). Of note, the level of activation in the contralateral primary sensorimotor cortex demonstrates the greatest difference between the val/val and val/met genotypes (Kim, Quinlan, Gramer, et al., 2016).

The presence of the Val66Met SNP may limit the potential benefits of the BDNF response following post-stroke rehabilitation (Mang et al., 2013). The likely reduced production of BDNF following rehabilitation, evident among people with stroke with the Val66Met polymorphism, may result in smaller improvements when compared to those who do not possess any BDNF polymorphism (Balkaya & Cho, 2019). It appears there may be a strong correlation between Val66Met presence and functional (Braun et al., 2020; Han et al., 2020; Hopkins et al., 2012; Kim, Park, Chang, et al., 2016) and cognitive status after stroke rehabilitation (Han et al., 2020). Post-stroke rehabilitation may result in poorer mRS outcomes (Braun et al., 2020), reduced functional and cognitive recovery (Han et al., 2020) or a slower rate of recovery to achieve a similar functional status as people with stroke who do not possess the Val66Met SNP (Helm et al., 2016). Other studies demonstrate no association (Bembenek et al., 2020; Cramer et al., 2022; Mirowska-Guzel et al., 2014) or a positive correlation at 7 days but not 30 days (Mirowska-Guzel et al., 2012) between Val66Met polymorphism and functional recovery post-stroke.

2.3.3 Effect of exercise on BDNF after stroke

Much of the understanding of the mechanisms involved in the activity-dependent increased secretion of BDNF concentration associated with exercise arises from research in animal models (Alcantara et al., 2018; Ploughman & Kelly, 2016; Ploughman et al., 2009). This pre-clinical work demonstrates moderate-to-high intensity aerobic exercise is needed to

increase BDNF in the brain (Alcantara et al., 2018). It has been proposed that a program of high intensity aerobic exercise can increase BDNF concentration in the hippocampus (Ploughman et al., 2015). A program comprising 30-minutes of progressive moderate intensity aerobic exercise (40-60% heart rate maximum) completed on most days per week for two to four weeks, commencing one to seven days after stroke is recommended to increase BDNF concentration in rodents (Ploughman et al., 2009; Ploughman et al., 2015). Mixed effects of functional training on BDNF concentration have been observed (Alcantara et al., 2018). Despite the pre-clinical findings, the optimal exercise intervention to elicit increased circulating BNDF in humans is unknown.

The effect of different exercise interventions on BDNF concentrations in the post-stroke population, including varied intervention durations, modalities, and intensities, has been explored (Boyne et al., 2020; Chaturvedi et al., 2020; Ryan et al., 2019). Yet no clear exercise recommendations exist to facilitate increased BDNF concentration in a human stroke population. It has been proposed that a program comprising 20 to 50-minutes of moderate-to-high intensity aerobic exercise (60-80% heart rate maximum) completed on three to five days per week for nine weeks, commencing a minimum of 70 days after stroke (Ploughman & Kelly, 2016) can produce positiive benefits on executive function (Ploughman & Kelly, 2016), which is linked to BDNF concentration (Leckie et al., 2014). For carriers of the Val66Met polymorphism, who may experience reduced BDNF concentration at rest and after exercise, more intense exercise may be required to elicit the same effects as those without this polymorphism (Mang et al., 2013).

Differences in study design, and how studies are reported, has likely contributed to the uncertainty regarding optimal exercise interventions to increase BDNF concentration. Differences in participant cohorts (i.e., stroke type, time post-stroke) (Alcantara et al., 2018; Limaye et al., 2021), and BDNF analysis techniques (i.e., use of the Enzyme-Linked Immunosorbent Assay (ELISA) or Western Blotting methods) may impact the changes in BDNF concentration observed following exercise (Limaye et al., 2021). These differences further cloud our understanding of the impact of stroke type on BDNF concentration (Limaye et al., 2021) and the ability to reproduce the intervention provided (Walker et al.,

2017). This program of research will explore how variations in exercise training parameters affect BDNF concentration after stroke.

While the relationship between BDNF concentration, aerobic exercise intensity and rehabilitation outcomes appear promising, measuring BDNF is not easy in clinical settings. A more cost effective, simple, and feasible alternative biomarker may be recommended for use in clinical practice to observe the effectiveness of rehabilitation interventions. Therefore, this program of research will explore the relationship between BDNF and lactate concentration, accounting for the effect of the Val66Met polymorphism.

2.4 Lactate

Lactate is a signalling molecule associated with various neurological processes, including synaptic plasticity and brain excitability (Herrera-Lopez & Galvan, 2018), memory and learning (Hu et al., 2021; Margineanu et al., 2018). Capillary blood lactate is also commonly used with healthy populations as a measure of exercise intensity (Hu et al., 2021; Schiffer et al., 2011; Tsukamoto et al., 2015; Tsukamoto et al., 2016).

Increased lactate concentration has been found following high intensity exercise, synthesised as a by-product of muscle glycolytic pathways, and released via astrocytic glycogenolysis (Skriver et al., 2014). The net uptake of lactate into the brain is markedly increased in response to increased blood lactate concentrations following high intensity aerobic exercise in a healthy cohort (Ide et al., 2000; van Hall, 2010). Monocarboxylate-transporters, whose expression is elevated as a result of high intensity exercise, catalyse lactate diffusion within the body, resulting in increased systemic lactate concentration and the transportation of lactate across the blood-brain barrier (Bergersen et al., 2015; Bergersen et al., 2007). Monocarboxylate-transporter 1 is found on the endothelial cells of cerebral blood vessels at the blood-brain barrier, with an intermediate to high affinity for lactate (Bergersen, 2015). Here, lactate works as a volume transmitter, whereby lactate diffuses down its concentration gradient, entering the brain to lactate receptor sites via extra- and intra-cellular compartments (Bergersen, 2015). As lactate can cross the blood-brain barrier, this substrate can be utilised by the brain as an alternative energy source

(Schurr, 2014) and is associated with improved memory function in rodent models (Suzuki et al., 2011). However, the association between lactate and memory function in a healthy or stroke human cohort is unclear.

Studies with humans indicate that lactate is an important substrate for neural function (Skriver et al., 2014; Wyss et al., 2011). Lactate has been associated with increased motor cortex excitability (Taubert et al., 2015) and is important for the maintenance of long-term potentiation (Skriver et al., 2014; Suzuki et al., 2011), contributing to improved long-term memory formation (Skriver et al., 2014; Taubert et al., 2015) and learning processes (Scavuzzo et al., 2020).

2.4.1 Association between lactate and BDNF

A positive correlation between lactate and BDNF concentration has been shown in rodent (Coco et al., 2013) and healthy adult cohorts (Schiffer et al., 2011). A clear understanding of the interaction between BDNF and lactate though is not yet fully understood, however it is proposed that lactate may induce the pathway by which BDNF is produced (El Hayek et al., 2019). The upregulation of BDNF gene expression facilitated by increased lactate concentration may therefore increase BDNF secretion and potentially enhance neuroplasticity (Mueller et al., 2020).

It is unclear whether the increase in lactate following high intensity exercise directly increases BDNF concentration or is due to other associated processes (e.g., changes in pH and blood gases) (Schiffer et al., 2011). Therefore, lactate has been referred to as a 'pseudo-hormone' that facilitates the upregulation of BDNF secretion following exercise (Schiffer et al., 2011). Further exploration is needed, even in healthy cohorts.

2.4.2 Relationship between lactate, BDNF and exercise

Higher concentrations of blood lactate are observed following high intensity aerobic exercise (Hermansen & Stensvold, 1972; Hu et al., 2021). Increases of approximately 8-15mM from baseline concentrations are possible after HIIT in rat cohorts (Coxon et al., 2018; Hu et al., 2021). Few studies have explored the relationship between lactate, BDNF,

and exercise in humans. In one study, significantly higher blood lactate concentrations were evident following HIIT compared to moderate intensity continuous training (Tsukamoto et al., 2015). In a study of 28 healthy males, no significant correlation was found between BDNF and lactate after acute bouts of low ($r = 0.03$, $p = 0.882$) or moderate ($r = 0.12$, $p = 0.54$) intensity exercise (Antunes et al., 2020). Though a significant inverse relationship between BDNF and lactate concentration was evident following an acute bout of high intensity aerobic exercise ($r = -0.38$, $p = 0.044$) (Antunes et al., 2020). Similarly, in a study of 15 participants (four female), a significant correlation between the change of BDNF and lactate concentrations was found following a graded exercise test ($r = 0.57$, $p < 0.05$) (Ferris et al., 2007). However, neither of these studies were powered to detect changes in BDNF and/or lactate concentration A large increase in lactate and BDNF concentrations were observed following a ramped protocol in a study conducted in eight male participants (Rojas Vega et al., 2006). However, this study did not explore the correlation between the BDNF and lactate concentrations.

There appears to be some evidence supporting high aerobic exercise intensity, BDNF and lactate concentrations and cognitive function. In people with chronic stroke, higher blood lactate concentration was associated with faster inhibition response, a domain of executive cognitive function (Palmer et al., 2022). Additionally, improvements in executive functioning were maintained for longer following HIIT compared to moderate intensity continuous training in healthy populations, but BDNF concentration was not measured (Tsukamoto et al., 2015; Tsukamoto et al., 2016). The relationship with BDNF was not measured in these studies.

It is plausible to suggest that the increase in blood lactate in response to increasing intensity of aerobic exercise in close temporal proximity exercise may facilitate a nonconscious learning process (Stoykov et al., 2017). The exhaustive nature of high intensity exercise may also result in increased serum cortisone levels, which are associated with increased stress and may have a negative effect on BDNF concentrations (García-Suárez et al., 2020). Though this is yet to be tested in people with stroke.

The measurement of BDNF concentration requires venous blood sampling, which is an invasive procedure requiring the removal of a minimum of 8mL of blood from the median cubital vein and costly BDNF analysis techniques. Blood lactate sampling is less invasive and requires only a small pinprick to the finger (El Hayek et al., 2019; Hu et al., 2021) and typically requires only a few drops of blood (0.3μL). Blood lactate analysis is also cheaper and quicker, uses reliable and valid hand-held analysers (Crotty et al., 2021) which are already used in many clinical practices (El Hayek et al., 2019; Hu et al., 2021). This program of research aimed to explore the relationship between aerobic exercise, lactate and BDNF concentration within the post-stroke population, while accounting for the presence of the Val66Met polymorphism, to determine if lactate may represent a potential alternative for the monitoring of neuroplasticity within clinical practice. However, due to the Covid-19 pandemic, which resulted in stringent lockdowns in NSW (where this research was conducted) and high staff turnover at the recruitment hospital, this study focused on a healthy cohort instead.

2.5 Exercise training after stroke

Physical activity, which can be defined as any movement that raises energy expenditure above resting metabolic rate (Caspersen et al., 1985), is recommended for all people with stroke to ensure optimal health and wellbeing and can be described on a continuum from sedentary to vigorous (Fini et al., 2017; Billinger et al., 2014). Exercise is defined as a subset of physical activity that entails 'structured and planned movements for the purpose of health' (Caspersen et al., 1985). In this program of research, the term physical activity will include recreational, leisure and incidental activity, and exercise will be used to describe structured interventions.

Regular exercise is one of the strongest predictors of reducing stroke occurrence (Turan et al., 2017). However, many people with stroke are highly inactive, creating a negative cycle of deconditioning associated with decreased function and increased risk of cardiovascular events (e.g., secondary stroke) (Gaskins et al., 2019). People with stroke have lower activity, completing fewer steps per day (4078 compared to 8338) (Fini et al., 2017), and energy expenditure levels (Kramer et al., 2016) than a healthy age-matched population. Survey data

from people with stroke demonstrate a reduction in exercise engagement when comparing pre- and post-stroke involvement (Shaughnessy et al., 2006) as well as adherence to community-based exercise programs (Miller et al., 2017). Given the direct link between exercise and stroke risk (Preston et al., 2017), exercise training is recommended as part of a comprehensive and multidisciplinary stroke rehabilitation program to optimise recovery (MacKay-Lyons et al., 2020). Exercise is feasible and beneficial during all phases of stroke recovery (Fini et al., 2021; Rose et al., 2011; Tang et al., 2009) and should incorporate a variety of exercise modalities (e.g., aerobic, resistance, neuromuscular and flexibility) to elicit the greatest benefit (Billinger et al., 2014; Tiozzo et al., 2015). Exercise is considered beneficial for numerous physical and psychosocial health domains post-stroke (Billinger et al., 2014), including cardiovascular health, cognition, impairment recovery, and neuroplasticity (Kramer et al., 2019). Improvements in these domains are associated with increased ADL completion (Pang et al., 2006) and health-related QoL post-stroke (Rosenfeldt et al., 2019). Exercise interventions provided to people with stroke should be individualised, accounting for each person's stage of stroke recovery, motor function impairments and subsequent safety concerns, exercise tolerance (i.e., level of fitness), exercise preferences as well as available support (Billinger et al., 2014).

Exercise training recommendations are commonly reported using the 'FITT Principle' to help guide health professionals, such as exercise physiologists and physiotherapists, in the development of individualised and evidence-based exercise prescriptions (Liguori et al, 2021). FITT refers to the frequency, intensity, time, and type of exercise to be completed. Table 2-1 (Moore et al., 2016; Liguori et al, 2021) describes the FITT principle, including 'Progression' which is considered the fifth principle of exercise prescription.

Table 2-1 Components of the FITT principle for exercise prescription (Moore et al., 2016; Liguori et al, 2021)

Frequency	Number of sessions in a certain period of time (e.g., week, month).
Intensity	Subjectively or objectively measured level of exertion during exercise.
Time	Duration of the session.
Type	Modality of exercise.
Progression	How the exercise is advanced to ensure further benefits because of continued training.

Specific FITT principles have been developed for the post-stroke population, collating evidence from numerous exercise interventions to create recommendations for an array of exercise modalities that are safe and beneficial for people with stroke (Billinger et al., 2014; MacKay-Lyons et al., 2020).

2.5.1 Aerobic exercise recommendations after stroke

Aerobic exercise is an umbrella term for large-muscle group activity that is rhythmic and sustained continuously (Billinger et al., 2014; Gaskins et al., 2019). Aerobic exercise can include endurance activities such as walking, cycling, and swimming as well as recreational activities such as racquet sports and soccer (Liguori et al, 2021). Post-stroke exercise recommendations are described in Table 2-2 (Billinger et al., 2014).

To achieve the high intensity of aerobic exercise required to facilitate neuroplasticity and cardiovascular benefits, interval training is recommended. Initially developed for people with cardiovascular disease, interval training comprises repeated bouts of short-duration higher intensity aerobic exercise interspersed with periods of lower intensity exercise to facilitate active recovery (Mezzani et al., 2012). Interval training produces greater improvements in cardiovascular function (Rognmo et al., 2004; Wisløff et al., 2007) and endothelial function (Cornish et al., 2011) in individuals with coronary artery disease and heart failure than continuous moderate intensity exercise (Mezzani et al., 2012).

Table 2-2 Aerobic exercise FITT principle post-stroke (Billinger et al., 2014)

Frequency	Minimum 3-5 days per week, aiming for 7 days per week as tolerated.
Intensity	'Moderate' intensity: • 40-70% VO_2R • 55-80% HR_{max} • 11-14/20 RPE (Borg, 1970)
Time	Cumulative total of 60 minutes per session as tolerated (e.g., 3x 10-minute bouts). Inclusion of a warm-up and cool-down of approximately 5-10 minutes each at the beginning and end of each session, respectively.
Type	Walking, stationary cycle ergometry, arm ergometry, arm-leg ergometer or functional seated exercises. Prescription should consider level of impairment, presence of comorbidities, fitness level, time post-stroke, and patient preference.
Progression	One principle changed at a time to ensure the workload is not increased too quickly. It is recommended that frequency or duration is increased initially, followed by an increase in intensity. 'Advanced' aerobic exercise might be defined as: F: 5-7 days per week I: 60-80% HRR or 14-16/20 RPE T: 20-60 minutes per sessions T: Large-muscle activities (e.g., walking, stationary cycling)

Abbreviations – HR_{max}: Heart rate maximum; HHR: Heart rate reserve; RPE: Rate of perceived exertion; VO_2R: Maximal oxygen uptake reserve.

In recent years, HIIT has emerged as a promising mode of delivery of high intensity aerobic training within the stroke population (Crozier et al., 2018; Gjellesvik et al., 2021). HIIT is considered safe in stroke rehabilitation (Boyne et al., 2023; Crozier et al., 2018; Gjellesvik et al., 2021), though medical clearance (Macko et al., 2016) and pre-exercise stress tests with ECG monitoring (MacKay-Lyons et al., 2020) are recommended to further ensure participant safety. High intensity aerobic exercise may be difficult to achieve and sustain in a stroke population (Boyne et al., 2023). This may be associated with the reduced cardiorespiratory fitness and increased energy expenditure evident after stroke (Kramer et al., 2016; Ploughman & Kelly, 2016). Therefore the lower intensity intervals within HIIT may be useful

to promote active recovery (Boyne et al., 2023). Guidelines for HIIT prescription and monitoring have been developed for people with cardiovascular disease (Taylor et al., 2019), however, HIIT is not commonly prescribed post-stroke (Boyne et al., 2017) or included in post-stroke exercise recommendations (Billinger et al., 2014; MacKay-Lyons et al., 2019). Table 2-3 outlines potential HIIT recommendations using the FITT principles currently evident in the literature, though the evidence is limited at this stage (Crozier et al., 2018). Crozier and colleagues (2018) provided a synthesis of evidence, proposal of preliminary considerations, and potential clinical implications for the use of HIIT within a post-stroke population. Although this systematic review is now five years old and is not a clinical guideline or meta-analysis, this paper provides insight into the current state of evidence supporting the use of HIIT after stroke.

Table 2-3 Current uses of HIIT in the literature post-stroke (Crozier et al., 2018)

Frequency	2-5 days per week for 2-4 weeks.
Intensity	85-95% HRR during 'active' phase. No clear recommendations for 'recovery' phase.
Time	Total session time of 25-30 minutes. On period to off period ratio can range from 30 seconds:30-60 seconds to 3 minutes:4 minutes. For example – four minutes 'on' repeated four times, three minutes 'off' three times (Askim et al., 2014).
Type	Treadmill, cycle ergometer or recumbent stepper, whichever is safer if the intervention is monitored.
Progression	Unclear at this time.

Abbreviation – HRR: Heart rate reserve.

Benefits of aerobic exercise post-stroke

Aerobic exercise can facilitate improvements in general health (Billinger et al., 2014) and mitigate the negative outcomes associated with stroke (Crozier et al., 2018; Gjellesvik et al., 2021; Gjellesvik et al., 2012; Wrann et al., 2013). Aerobic exercise can help manage blood pressure (Gaskins et al., 2019), improve vascular health (MacKay-Lyons et al., 2020) and induce cardioprotective benefits such as endothelial health to reduce the risk of

cardiovascular events (Billinger et al., 2014). Participation in aerobic exercise is suggested to reduce secondary stroke risk (Han et al., 2017).

Other stroke-specific benefits following aerobic exercise include increased walking efficiency and exercise tolerance (Billinger et al., 2014; MacKay-Lyons et al., 2020), improved brain health and cognitive function (Wrann et al., 2013), as well as reduced depressive symptoms (Eng & Reime, 2014). In addition, high intensity aerobic exercise (e.g., HIIT) is associated with increases in neurotrophins (e.g., BDNF) which may contribute to increased neuroplasticity (Crozier et al., 2018) and may facilitate greater motor skill retention following stroke rehabilitation (Nepveu et al., 2017). The benefits of aerobic exercise are further associated with reductions in motor impairment, increased independence in ADLs (Billinger et al., 2014; Gjellesvik et al., 2021; Gjellesvik et al., 2012), and improvements in QoL (MacKay-Lyons et al., 2020).

2.5.2 Potential barriers to exercise training after stroke

Potential barriers to exercise training span a variety of domains comprising of patient-related, environmental (Billinger et al., 2014; Espernberger et al., 2021) and clinician-related barriers (Gaskins et al., 2019). Patient-related barriers may include the presence of comorbidities, negative beliefs about exercise, a lack of perceived control in one's own healthcare, lack of awareness of available resources, cost of interventions (Nicholson et al., 2014; Simpson et al., 2011), and lack of motivation (Damush et al., 2007; Rimmer et al., 2008). Environmental barriers include a lack of transportation, program costs, access to information, or the lack of a support system to facilitate engagement in exercise (Damush et al., 2007; Rimmer et al., 2008; Simpson et al., 2011). Clinician-related barriers include staff experiencing reduced self-efficacy for the delivery of appropriate interventions and reduced confidence to adapt exercise interventions to the patient's impairment (Condon & Guidon, 2018; Moncion et al., 2020).

A clear understanding of these potential barriers, and their effect on the capacity of a person with stroke to engage in exercise, is needed to identify possible solutions to optimise engagement in exercise interventions post-stroke (Gunnes et al., 2019). Engaging friends and family in exercise, prescribing exercises that mimic favoured recreational activities

(Espernberger et al., 2021) and continued professional development for clinicians (Sadler et al., 2017) are evidence-based approaches to overcoming such barriers. While extensive research has been conducted on the potential barriers and facilitators to participating in (Simpson et al., 2011), and the recommendation/ prescription of, exercise after stroke (Moncion et al., 2020), little evidence exists for high intensity exercise specifically. This program of research will explore the barriers, and potential facilitators, to the implementation of HIIT in clinical practice.

2.6 Upper limb rehabilitation after stroke

Post-stroke motor rehabilitation aims to facilitate 'motor learning' and reduce disability via changes in motor behaviour due to changes in the structure and function of the central nervous system (Langhorne et al., 2011; Mang et al., 2013). Rehabilitation can facilitate functional recovery beyond the window of spontaneous recovery by targeting the unique capacity of the central nervous system to undergo motor reorganisation (Teasell et al., 2020) and translate to increased motor function (Pollock et al., 2014). One common upper limb rehabilitation intervention includes Constraint-Induced Movement Therapy (CIMT) which can facilitate increased use of the upper limb post-stroke (Fleet et al., 2014).

2.6.1 Constraint-Induced Movement Therapy

CIMT is a valuable upper limb rehabilitation intervention following stroke (Rocha et al., 2021). CIMT is comprised of four main components which facilitate the forced use of the paretic upper limb as described in Table 2-4 (Taub et al., 2006; Taub et al., 2013).

Table 2-4 Four main components of Constraint-Induced Movement Therapy (CIMT) (Taub et al., 2006; Taub et al., 2013)

Main components of CIMT interventions:
(1) Intensive and graded use of the paretic limb during task-specific movements of the upper limb. Duration or paretic limb use progressively increase towards six hours per day, usually for a two-week period.
(2) Training by shaping, a method of training in which motor tasks are broken down into small, stepwise components which are trained in isolation. When deemed capable, these components are progressively assembled to allow the individual to practice the movement in its entirety.
(3) Constraint of the non-paretic upper limb, often through the wearing of a mitt or glove, for approximately 90% of waking hours. The forced use of the paretic limb during the completion of functional upper limb movements aim to drive neuroplasticity (McCluskey et al., 2020) to facilitate greater real-world use of the limb (Miltner et al., 2016).
(4) Transfer package which incorporates behavioural methods to promote the transfer of therapeutic gains from the clinical setting to daily life. Such strategies may include behavioural contracts, problem-solving strategies to overcome perceived barriers, home skill assignments, daily home diary or daily completion of the Motor Activity Log to promote to monitor paretic limb use.

Electroencephalography studies have shown forced use of the paretic upper limb facilitates the expansion of cortical representation of the muscles of the paretic limb (Liepert et al., 2000; Liepert et al., 2004; Mark et al., 2006; Sawaki et al., 2014). The increased cortical map size after CIMT is associated with improved Motor Activity Log (MAL), Action Research Arm Test (Doussoulin et al., 2018) and Wolf Motor Function Test (WMFT) (Sawaki et al., 2014) scores from baseline. These improvements in post-intervention scores represent increased patient-perception of paretic limb use (Doussoulin et al., 2018; Taub et al., 2013), improved paretic limb function (Doussoulin et al., 2018; Hsieh et al., 2009; Yozbatiran et al., 2008) and greater amount of use of the paretic limb (Hsieh et al., 2009; Sawaki et al., 2014). Such improvements may translate to positive benefits in the amount, quality, and precision of upper limb use post-stroke with reduced effort (Doussoulin et al., 2018; Kwakkel et al., 2015). CIMT has also been demonstrated to improve the efficiency of ADL completion which

is associated with increases in QoL (Kwakkel et al., 2015) and independence (Abdullahi et al., 2020). CIMT has been demonstrated to be beneficial in the chronic phase of stroke recovery (Taub et al., 1994). However, it was not more effective than traditional therapy in the acute phase and instead diminished motor improvement when started early after stroke (Dromerick et al., 2009). Despite the known benefits of CIMT, it is labour- and resource-intensive intervention for the patient and clinician, respectively (Abdullahi, 2018; Fleet et al., 2014; Page et al., 2004). Therefore, modified interventions, which are based upon the main components of CIMT but with variations in the nature of the exercises, and durations of the intervention sessions and tasks, can be implemented (Nijland et al., 2013).

2.6.2 Modified Constraint-Induced Movement Therapy

When compared to CIMT, mCIMT demonstrated significantly greater improvements in motor control and functional gains (Shi et al., 2011; Smania et al., 2012; Wu et al., 2007). Enhanced ipsilesional cortical excitability and larger motor-evoked potentials (MEPs; electrical signalling during movement) may also be facilitated following mCIMT interventions (Yu et al., 2017). Functionally, improved motor function of the paretic limb and cortical reorganisation facilitated by mCIMT may be associated with increased paretic limb use in daily life (Shi et al., 2011), with positive effects being maintained for longer durations (e.g., 4 weeks post-intervention) (Wang et al., 2011). The benefits of mCIMT have been demonstrated during the acute (Page et al., 2005; Yu et al., 2017), early- (Page et al., 2005; Page et al., 2004; Wang et al., 2011) and late-subacute (Page et al., 2004; Page et al., 2001) and chronic phases of stroke recovery (Baldwin et al., 2018; Page et al., 2004; Smania et al., 2012; Szaflarski et al., 2006; Wu et al., 2012).

Exercise may be used to facilitate increased concentrations of circulating biomarkers of neuroplasticity (e.g., BDNF) in close temporal proximity to motor rehabilitation to enhance rehabilitation outcomes (Valkenborghs et al., 2019). For example, the benefits of mCIMT may be extended upon by exercising immediately prior to, or after, motor rehabilitation. This program of research will propose the use of a combined aerobic and mCIMT intervention to explore functional benefits in upper limb use.

2.6.3 Measurement of improvement with upper limb rehabilitation

To identify changes in upper limb use outside of the clinical setting, a significant goal of CIMT and mCIMT, the MAL (Uswatte et al., 2006) and Rating of Everyday Arm-Use in the Community and Home (REACH) scales were developed (Simpson et al., 2013). The MAL comprises two scales, the MAL Amount of Use (MALAOU) and MAL Quality of Movement (MALQOM), that cover a range of activities including personal care and ADLs. Together, the MALAOU and MALQOM are a 30-item scale that assesses how much and how well the participant uses their paretic limb in their home (Uswatte et al., 2006). The MALAOU is scored using a six-point ordinal scale, with a zero indicating non-use, and a five indicating use of the paretic limb as often as before stroke (Taub et al., 2011). The MALQOM is also scored using a six-point ordinal scale, with a zero indicating the paretic limb is never used, and a five indicating the ability to use the paretic limb is as before the stroke (Taub et al., 2011).

The MAL-30 was developed by researchers as a subjective assessment of real-life paretic upper limb use (Taub et al., 1993), commonly used to determine the effect of CIMT or mCIMT programs on paretic upper limb use (Li et al., 2012; Page, 2003). A minimal detectable change of 0.67 to 1.27 points is demonstrated in stroke populations (Simpson et al., 2013); however, the minimal clinical important difference (MCID) varies across the spectrum of recovery (van der Lee et al., 2004). An increase of 1 to 1.1 points is considered a MCID (Lang et al., 2008), however an increase of 0.5 points is considered important in the chronic phase of recovery (van der Lee et al., 2004). The MAL is considered to have excellent correlation with other measures of paretic upper limb function after stroke (i.e., Stroke Impact Scale hand function), however this was examined using the MAL 28-item scale (Uswatte et al., 2005).

While the MAL is a valid tool to quantify paretic limb function after stroke (Uswatte et al., 2006), responsiveness to changes in function due to therapy may vary. Large effect sizes are evident in the early stages of stroke recovery (e.g., acute versus subacute) and in individuals with less severe impairments (Simpson & Eng, 2013). The MAL-30, especially when utilising the MALAOU and the MALQOM subscales, is time-consuming in clinical settings. MAL instructions outline the need to complete the MAL-30 at screening, one-week later at

baseline (i.e., before the therapy program) and at completion of the program (Taub et al., 2011). Numerous versions of the MAL exist, including the 14, 20, 26 and 30-item scales, with inconsistencies across the stroke literature (van der Lee et al., 2004). Thus, the interpretation of the effects of interventions must account for the number of MAL items studied. While improvements in MAL scores post-intervention are positive, the score does not provide details regarding the specifics of how the movement is conducted (i.e., paretic limb is only used for stabilisation, or it is able to produce manipulation (Simpson et al., 2013)). Nor does it account for any impact of dominance/non-dominance on performance.

The REACH provides two classification scales, one each for the dominant and non-dominant upper limb, developed by people with stroke, caregivers, and clinicians (Simpson et al., 2013). Each classification category is attributed to levels of function considered meaningful for people with stroke, caregivers, and clinicians (Simpson et al., 2013). An increase of one level is considered the MCID of the REACH following therapy (Simpson et al., 2013). Positive, statistically significant correlations have been demonstrated between the REACH and measures of activity and participation, thus increasing translation to daily life (Obembe et al., 2023). The REACH is a reliable and valid measure of paretic upper limb use in the real world (Simpson et al., 2013). It is quick to administer and is highly correlated with the MAL 14-item amount of use scale (Simpson et al., 2013), therefore supporting its use in clinical practice. There is a strong correlation between the MAL and the REACH (Simpson et al., 2013), though this study was conducted in a Canadian cohort. Additionally, no study has explored the relationship between the MAL and the REACH following a CIMT or mCIMT intervention. This program of research will explore the correlation between the MAL and REACH to if the REACH can be used as a quicker assessment of upper limb use in clinical practice.

The Fugl-Meyer Assessment Upper Extremity subscale is another assessment of motor function in people with stroke who present with hemiparesis (Fugl-Meyer et al., 1975). This assessment is one of the most used assessments of motor impairment following stroke (Gladstone et al., 2002) and is recommended by the Stroke Recovery and Rehabilitation Roundtable to assess body function and structure (Kwakkel et al., 2017). The Fugl-Meyer Assessment Upper Extremity subscale has excellent inter-rater reliability in the post-stroke

population (See et al., 2013; Sullivan et al., 2011). In addition, MCID have been established for the Fugl-Meyer Assessment Upper Extremity subscale to allow the results of this study to be compared to values considered important for clinical practice. An increase of 5.25 points in this assessment is considered clinically important for chronic people with stroke (Page et al., 2012).

2.6.4 Optimising upper limb rehabilitation after stroke

One emerging treatment option is the use of aerobic exercise to augment upper limb improvements (Quaney et al., 2009). Aerobic exercise has been used as a primer for upper limb motor rehabilitation post-stroke (Valkenborghs et al., 2019). This method is grounded in the evidence suggesting that BDNF is released in an activity-dependent manner (Knaepen et al., 2010; MacLellan et al., 2011). That is, aerobic exercise may facilitate increased BDNF concentration, which is associated with neuroplastic changes within the brain (Marosi & Mattson, 2014; Ploughman et al., 2015). Increased neuroplasticity attributed to greater BDNF concentrations are further associated with reductions in neurological deficit and may facilitate improvements in function following post-stroke motor rehabilitation (Berretta et al., 2014; Lindgren & Maguire, 2016). However, it is suggested that the increased systemic BDNF concentration following aerobic exercise may return to baseline approximately one-hour after the cessation of exercise (Knaepen et al., 2010). In a healthy adult population, aerobic exercise (e.g., stationary cycling) has been shown to moderate upper limb cortical excitability, which may prime the motor cortex for plasticity (Singh et al., 2014). Aerobic exercise, when combined with skill training, increases the cortical representation of the target muscle to a greater degree than skill training alone (Singh et al., 2016). It is believed this increase in neuroplasticity may facilitate increased learning and functional gains associated with upper limb training (Singh et al., 2016). This program of research will propose the use of aerobic exercise to supplement intensive upper limb rehabilitation and explore the timing (i.e., pre- or post-rehabilitation) of the intervention to optimise functional benefits.

Combined interventions for upper limb rehabilitation post-stroke

For aerobic exercise to act as a primer for motor skill acquisition post-stroke, exercise and skill training must be completed in close temporal proximity to one another (Mang et al.,

2014; Nepveu et al., 2017; Roig et al., 2013). However, it is unclear if greater functional outcomes result from exercise performed immediately before or after rehabilitation (Nepveu et al., 2017; Roig et al., 2012; Skriver et al., 2014; Snow et al., 2016; Thomas et al., 2016; Valkenborghs et al., 2019).

Valkenborghs et al. (2019) explored the effect of HIIT prior to task-specific training of the upper limb, compared to task-specific training alone on upper limb outcomes, in a stroke population. The group that completed HIIT plus task-specific training completed fewer upper limb repetitions compared to the task-specific training only group (158 ± 49 versus 208 ± 8 in the task-specific training only group) (Valkenborgh et al., 2019). Additionally, larger improvements in WMFT scores were observed post-intervention in the combined intervention (Valkenborghs et al., 2019). In qualitative interviews with participants post-training, the participants reported the intensity of the aerobic exercise completed before the task-specific training may have compromised their ability to complete a higher number of upper limb repetitions (Valkenborghs et al., 2019). This diminished capacity may be the result of participants in the HIIT + task-specific training group experiencing greater amounts of fatigue compared to the task-specific training only group (3.5 ± 0.7 out of 10 versus 1.7 ± 1.4 out of 10) (Valkenborghs et al., 2019). In the Nepveu et al. (2017) study, 22 people with stroke completed five blocks of hand-grasp skill practice interspersed with 15-minutes of HIIT training or 15-minutes of rest to score skill acquisition and retention (Nepveu et al., 2017). The authors reported no difference in motor skill acquisition at the end of the five blocks of skill practice in the group who rested ($p = 0.42$). However, the group that completed hand-grasp skill practice + HIIT demonstrated significantly better skill retention at 24 hours after training when compared to the group that completed the skill training + rest ($p = 0.04$) (Nepveu et al., 2017). Fatigue was again reported by participants as a side effect of the interventions, though no objective measure was reported. Whether the participants fatigue levels affected their performance of the intervention or outcome measures was unclear. Therefore, the ordering of exercise and skill training may influence fatigue levels and subsequent number of motor training repetitions completed warranting further investigation.

Chapter 3 IMPACTS OF COVID-19

This program of research was commenced on 1st March 2021 at Australian Catholic University (ACU), Strathfield, New South Wales (NSW) campus. At this time, Australia was in the second year of the Covid-19 pandemic, which was first recognised in early 2020. The pandemic resulted in a state-wide lockdown from 27th June 2021 to 11th October 2021 (106 days). During this time, a stay-at-home order forced all Greater Sydney residents to stay within a 5-kilometre radius of their home, except for approved work or medical appointments. From 23rd August 2021 to 11th October 2021 (49 days), Greater Sydney residents were also restricted to 60-minutes of outdoor exercise per day, with exercise facilities closed and masks to be worn while exercising outdoors. During this time the ACU Strathfield campus was also closed, with all business shifted to online and face-to-face research ceased. The campus re-opened on 27th January 2022, with research gradually returning to normal from this date.

In late 2020, the research team engaged with staff at Royal Rehab Private Petersham, a private rehabilitation facility in Sydney, to assist with participant identification and recruitment for this program of research. At the time no lockdown protocols had been discussed in NSW, and face-to-face research was continuing unhindered. However, as a result of the Covid-19 restrictions, members of the research team were unable to screen and recruit participants on-site. Instead, hospital staff were engaged to screen and recruit participants for the trial. During this time, the required sample size (n = 28) for the planned randomised controlled trial (RCT) was calculated by the research team and discussed with hospital staff in late 2020. Based on historical data for stroke admissions to Royal Rehab Private Petersham, the number of participants required for the RCT over the period of time planned to conduct the trial appeared feasible. Regular Zoom meetings were conducted, and emails were exchanged to plan and formalise screening and recruitment processes, and troubleshoot any issues. The recruitment pathway established involved hospital staff screening and approaching stroke patients, providing the participant information statement, and recording their name, phone number, email address and diagnosis if they were interested in participating in the study. This information was then to be emailed to the research team in a password-secured Microsoft Excel document to allow the research team

to contact prospective participants for final screening, consenting and involvement in the study. Ethics approval for the RCT was obtained from Royal Prince Alfred Hospital Human Research Ethics Committee (HREC) (X21-0432), Royal Rehab Research Governance Office (2021-ETH12179) and from ACU HREC (2022-2698RC).

As a result of the increasing infection rates and subsequent state-wide lockdown, research was de-prioritised in the hospital, and staff turnover and reassignment resulted in the RCT being put on hold. Therefore, alternative studies were developed to answer the overall research question of this program of research, while ensuring adequate recruitment rates and the completion of a quality program of research in a timely manner. Several ethics amendments were submitted to the relevant HREC's, which took time to complete and obtain approval. The recruitment methods of Study 2, 3 and 4 were amended to include social media and relevant conferences in the field of stroke rehabilitation, however, recruitment rates remained low. It is worth noting that the experiences of this research program were consistent with clinical research globally, with low participant recruitment rates (Sathian et al., 2020), reallocation of staff and the negative effects of the reliance on hospital staff to assist with recruitment and screening processes (Mourad et al., 2020).

As a result of the Covid-19 interruptions and following guidance from the supervisory team and the panel of experts at the Confirmation of Candidature on 6th October 2021, the original program of research was modified. The main point of concern raised at the Confirmation of Candidature was the feasibility of an in-person trial given the unknown nature of, and public health response to, Covid-19 and the potential impact of restrictions. The research candidate considered alternative studies which did not require in-person participation, ensuring the program of research could be completed despite ongoing restrictions in health research and potential future lockdown/s. These studies were still within the scope of work being proposed, focusing on factors that could increase participation in the RCT, which is hoped to be conducted at a later date. Consequently, a web-based questionnaire and semi-structured interview study was developed (Study 2, Chapter 6).

In early-2022, the recruitment hospital and ACU allowed face-to-face research to recommence, however, due to staff shortages, Royal Rehab Private Petersham did not have the capacity to continue screening and approaching potential participants. This meant potential participants admitted during the lockdown period could not be screened for this project. Recruitment may have also been impacted by fear surrounding Covid-19 transmission in the university where the research was to be conducted (Mirza et al., 2022). Therefore, the questionnaire and interview study proposed at the Confirmation of Candidature became a significant focus of this program of research due to the ongoing implications of Covid-19 experienced throughout the period of candidature. The protocol of the original RCT is presented in this thesis as the research team hope to undertake this study in the future (Study 5, Chapter 9). The final program of research is further discussed in Chapter 4 of this thesis.

Chapter 4 METHODOLOGY AND DESIGN

This chapter will explore the methods, design and setting of this program of research. Multiple research methods were used to investigate how personalised exercise can be provided to optimise functional outcomes post-stroke. This program of research included one systematic review (Chapter 5), one mixed-methods study (i.e., quantitative and qualitative) (Chapter 6) and two quantitative studies (Chapters 7 and 8).

This program of research addressed two main aims, (1) to identify optimal exercise training parameters to promote increased BDNF concentration after stroke, including barriers and facilitators of the optimal exercise intervention to use in clinical practice and (2) to explore the relationship between commonly used outcome measures of neuroplasticity and upper limb function.

Individual study chapters have been written with the intention of publication, including sufficient detail to allow replication of the methodologies used. Below outlines additional information that supplement the methods section of the individual study chapters within this thesis.

4.1 Study Design

Study 1 (Chapter 5) used systematic review and meta-analysis methods to investigate the effect of various exercise interventions on BDNF concentration post-stroke. Study 2 (Chapter 6) used a mixed-methods quantitative and qualitative methods to explore the barriers and facilitators to HIIT post-stroke from the perspective of people with stroke and health professionals who work with people with stroke. Study 3 (Chapter 7) used a pre-post observational method to investigate the effect of a submaximal graded exercise test on BDNF and lactate concentrations and the correlation between the biomarkers. Study 4 (Chapter 8) used a pre-post observational method to explore the relationship between the MALAOU, MALQOM Scale and the REACH scale. Study 5 (Chapter 9) presents a proposed RCT protocol to investigate the effect of a combined HIIT and mCIMT intervention compared to mCIMT alone on upper limb motor function recovery post-stroke.

4.2 Participants

Three different groups of participants were recruited to the studies within this doctoral research program: people with stroke, health professionals, and healthy adults.

People with stroke were recruited for participation in Study 2 and 4. To be eligible for inclusion in either study, people with stroke needed to: (1) have a diagnosis of single or multiple ischaemic and/or haemorrhagic stroke, (2) be aged ≥ 18 years, (3) live in Australia, and (4) understand written and verbal English language. Additionally, for Study 4, people with stroke needed to present with upper limb hemiparesis following a stroke with ≥10 degrees of active movement in the paretic shoulder, elbow, wrist and ≥2 digits. People with stroke were excluded from either study if diagnosed with receptive aphasia causing difficulty with understanding the requirements of the relevant study methods. For Study 4, people with stroke were also excluded if they were: (1) undertaking any other formal exercise training program during the study period, and/or (2) had a diagnosis of any other condition that may limit their participation in the research. The requirement to meet the Covid-19 vaccination requirements of ACU to participate in research, as per ACU HREC policy (Australian Catholic University, 2021), was added to the requirements for Study 4.

Health professionals were also recruited in Study 2. To be eligible for participation, participants needed to be: (1) qualified health professionals with experience working with people with stroke in a professional capacity, (2) aged ≥ 18 years, (3) working in Australia, and (4) able to understand written or verbal English language. There were no exclusion criteria.

Healthy adults were recruited for participation in Study 3. Initially, the intent of Study 3 was to investigate the relationship between BDNF and lactate at rest, after a submaximal graded exercise test and the change in concentration in people with stroke and an aged- and sex-matched healthy adult cohort. However, due to recruitment and methodological challenges because of the Covid-19 pandemic, the study was limited to healthy adults only. Adults were eligible if they: (1) were aged ≥ 18 years, (2) understood written and verbal English language, and (3) were cleared to participate in exercise using the Exercise and Sport Science Australia (ESSA) Adult Pre-Exercise Screening System tool (APSS, version 2, ESSA,

2019). Adults were excluded if they had a diagnosis of blood-borne infectious disease and/or diagnosis of other condition(s), acute or chronic, that may limit their ability and safety to participate (e.g., unstable cardiovascular disease, lower-limb conditions). The additional inclusion criteria to meet the Covid-19 vaccination requirements of ACU was added to the study methods.

4.3 Setting

Study 2 was conducted online, with questionnaires distributed via REDCap (Research Electronic Data Capture), an online research platform hosted by ACU, with participants residing in Australia. The semi-structured interviews of Study 2 were conducted online via Zoom. Study 3 and 4 were conducted across university health clinic settings. Data for all studies (Study 1-4) were analysed at the ACU Strathfield campus.

Royal Rehab Private Petersham (formerly MetroRehab Hospital until February, 2023)
Royal Rehab Private Petersham is a private rehabilitation facility offering multidisciplinary in- and out-patient services, including exercise physiology, physiotherapy, speech therapy and occupational therapy, to people with stroke in the late subacute and chronic phases of recovery. Royal Rehab Private Petersham is located in Petersham, NSW, within the Sydney Local Health District. Royal Rehab Private Petersham is approximately 20 minutes from the ACU Strathfield campus, which is also located within the Sydney Local Health District. People with stroke are commonly referred to Royal Rehab Private Petersham from Royal Prince Alfred Hospital, Camperdown for inpatient rehabilitation, in addition to self- or general practitioner referrals for outpatient rehabilitation. The research candidate had personal connections with Royal Rehab Private Petersham due to previous employment at the facility.

In Study 4, initially the Allied Health Manager and the Neurological Rehabilitation Care Coordinator at Royal Rehab Private Petersham screened all people with stroke admitted to the in- or out-patient program against the inclusion criteria to determine eligibility. While the plan was for members of the research team to assist in screening and recruitment, as a result of the Covid-19 pandemic, members of the research team were unable to enter Royal

Rehab Private Petersham. Therefore, the Allied Health Manager and the Neurological Rehabilitation Care Coordinator provided eligible participants with the participant information and consent form, and with approval from the potential participant, forward their contact details to the research team. However, as the impact of the Covid-19 pandemic escalated and metropolitan Sydney went into lockdown (June to October 2021), recruitment for the project was suspended. Staff turnover at Royal Rehab Private Petersham further impacted patient screening and recruitment in 2022 as the allied health staff were unable to add this demand to their busy workload.

Australian Catholic University

Study 3 and 4 were administered within the Exercise Lifestyle Clinic located within the ACU Strathfield Campus. The Exercise Lifestyle Clinic is a student-orientated health clinic, providing targeted exercise interventions to individuals who have, or who are at a high risk of developing chronic medical conditions. The clinic is operated by a team of Accredited Exercise Physiologists, supported by students undertaking a Bachelor of Sport and Exercise Science or a Master of Clinical Exercise Physiology. Clients are often self-referred or recommended to attend the clinic as part of a Chronic Disease Management Plan. Located within the Strathfield campus, the Exercise Lifestyle Clinic is approximately 20 minutes from Royal Rehab Private Petersham. The clinic boasts a range of high-quality equipment including numerous aerobic ergometers, pin-loaded weight machines, free-weights, balance training apparatus and bodyweight-supported treadmill setup.

Study 4 was also administered within the ACU Banyo Health Clinic, Brisbane. The Banyo Health Clinic is a teaching facility which provides allied health services to the general public, as well as to university staff and students. The ACU Banyo Health Clinic also deliver a CIMT Clinic, which encompasses a two-week clinic program of four hours per day (Monday to Friday) to assist with upper limb function after stroke. Participants are self-referred to the clinic which is led by Occupational Therapy students under the supervision of experienced Occupational Therapy Professional Practice Educators.

4.4 Recruitment

Participants for Study 2 and 3 were recruited via social media and personal networks of the research team. Social media avenues included the Centre of Research Excellence Stroke Rehabilitation and Brain Recovery newsletter, Facebook, Twitter/X, LinkedIn, the Australian Stroke Foundation website and relevant professional association social media (e.g., Australian Physiotherapy Neurology Special Group Facebook and ESSA NSW Chapter Facebook group). Conference poster presentations (i.e., Stroke Society of Australasia and Smart Strokes in 2021 to 2023) were also utilised to discuss potential recruitment. Personal networks of the research team included ACU campus staff and students, research networks and clinical networks.

For Study 4, people with stroke were recruited in Sydney, NSW and Brisbane, Queensland to participate in this study. Participants in NSW were recruited via Royal Rehab Private Petersham, following the completion of their in- or out-patient rehabilitation program. Staff at Royal Rehab Private Petersham provided the contact details of interested individuals to the research team upon discharge. A member of the research team contacted the individual via telephone to enrol them in the study. People with stroke participating in the CIMT clinic in Queensland were screened by a member of the research team and approached to participate if they met the study inclusion criteria. Individuals self-refer to the clinic, learning of the clinic from social media, local advertisements or mention by a member of their medical team.

4.5 Sample size

For Study 2, no specific target sample size was calculated, and a sample of convenience was recruited. Quantitative studies exploring the barriers to exercise participation after stroke recruited 50 people with stroke (Nicholson et al., 2017) and 33 health professionals who worked with people with stroke (Nathoo et al., 2018). Qualitative studies of the barriers to exercise participation after stroke recruited an average of 17 people with stroke (Nicholson et al., 2014) and 18 health professionals (Gaskins et al., 2021). Given the impact of the Covid-19 pandemic on research (Sathian et al., 2020) similar sample sizes were desired. For the quantitative component a sample of approximately 40 people with stroke and health

professionals each were anticipated. For the qualitative component, eight to ten participants for each group were desired. It was anticipated that these sample sizes would provide sufficient information to answer the research questions and data saturation would be achieved for the qualitative component (Hennink et al., 2017).

For Study 3, a sample of convenience was recruited. Previous studies exploring the correlation between BDNF and lactate concentration in response to an acute bout of aerobic exercise in healthy adults recruited between 15 (11 males and four females) (Ferris et al., 2007) and 28 (all males) (Antunes et al., 2020). Using G Power with moderate effect size of 0.6, significance level of 0.05 and a power of 80%, a minimal sample size of 24 participants were required to identify changes in BDNF concentration. The examination of potential confounders of BDNF concentration such as the presence of the Val66Met polymorphism (Helm et al., 2017), and sex (Wei et al., 2017) was achieved through subgroup analysis.

For Study 4, a sample of convenience was recruited. Sample size calculations were undertaken for the CIMT component of the RCT originally developed for this program of research. To identify the effect of a mCIMT program on upper limb skill acquisition, data from existing literature was used to input values into G Power. With an effect size of 0.8, significance level of 0.05 and a power of 80%, a minimal sample size of 15 participants were required to identify changes in MAL (McNulty et al., 2015). Participants were recruited from an existing pool of people recruited for existing projects or clinical services (i.e., research participants in Strathfield, and participants included in the CIMT Clinic in Banyo) within ACU Strathfield and Brisbane campuses.

Details regarding the procedure, outcome measures, and data analysis of Study 2, 3 and 4 are discussed below.

4.6 Study 2: High Intensity Interval Training POst-STroke (HIIT-POST): Stroke survivors' and health professionals' views

4.6.1 Procedure

Participants in Study 2 (i.e., people with stroke and health professionals who work with people with stroke), completed an online questionnaire exploring the barriers and facilitators to HIIT post-stroke. A subset of participants completed a semi-structured interview via Zoom to further explore the barriers and facilitators to HIIT after stroke.

A mixed-methods approach was used to gain a deeper and broader understanding of the views of HIIT after stroke using both quantitative and qualitative methods (McKim, 2017). The use of mixed-methods research is recommended to allow a comprehensive approach to complex research questions and are considered extremely useful when exploring potential changes in healthcare practices (O'Cathain, Murphy & Nicholl, 2007).

Two separate questionnaires were used in this study, one for people with stroke and one for health professionals who work with people with stroke. The questionnaires were developed following review of existing literature exploring barriers and facilitators to exercise after stroke, however these were not specific to HIIT (Boyne et al., 2017; Condon & Guidon, 2018; Débora Pacheo et al., 2021; Rimmer et al., 2008). Semi-structured interview scripts were developed by the research team and included open-ended questions to allow participants to voice any additional barriers and facilitators regarding HIIT after stroke that were not outlined in the questionnaire.

Promotional material (i.e., social media) used to advertise the study to potential participants included links (i.e., URL or QR code) directing potential participants to a participant information statement and self-screening questions hosted with the questionnaire on the REDCap platform. If the inclusion criteria (outlined in Chapter 4.2 Participants) (determined via the self-screening questions) of the study were met and e-Consent was provided, the individual was then directed to the questionnaire. Questionnaires were completed on REDCap, to allow for ease of use for the participants while ensuring the security of the confidential information collected (Patridge & Bardyn, 2018). The REDCap questionnaire

was created using large text, large buttons for answer selection, text-to-speech functionality and a 'save and return later' function to optimise ease of use, in accordance with the feedback provided by the lived experts. Upon completion of the questionnaire, participants were invited to complete an expression of interest form (including the provision of their email address) to participate in a semi-structured interview to provide further insight into their views of HIIT post-stroke.

Questionnaires

The questionnaire for people with stroke was co-designed by the research team (three exercise physiologists and one physiotherapist) with four lived experts, while the health professional questionnaire was co-designed by the research team with two lived experts (a basic physician trainee and an exercise physiologist). The inclusion of lived experts increased the relevance of the questions and outcomes, appropriateness of the study methods (Slattery et al., 2020) and supports the patient-centred approach characteristic of this research (Ioannidis, 2016). For both the people with stroke and health professional questionnaire, the research team developed an initial draft questionnaire, following a similar structure to existing questionnaires examining barriers and facilitators to exercise after stroke (Boyne et al., 2017; Drigny et al., 2019). The lived experts were then emailed Microsoft Word copies of the draft questionnaire to review and Zoom meetings conducted to allow the lived experts to provide feedback and recommendations regarding the topics covered and the content/wording of the questionnaires. Finalised questionnaires were input into REDCap, with the lived experts given further opportunity to provide additional feedback on the layout of the questionnaire in REDCap and the accessibility of the online platform (e.g., size of the font). Following final revision, the final version (i.e., REDCap link to the questionnaire) was sent to the lived experts for approval and to pilot the online questionnaire prior to release and distribution for data collection.

The outline of both questionnaires is presented in Table 4-1 (See Appendix 1 [people with stroke] and 2 [health professionals] for the full questionnaires). Closed and Likert-type style questions were used to collect demographic information, frequencies of response, and level of agreement with barrier and facilitators statements (Portney, 2020).

Table 4-1 Sections of the questionnaires

People with stroke	Health professionals
1. Demographic information. 2. Exercise habits before stroke. 3. Exercise habits after stroke. 4. Experience/interest in HIIT. 5. Barriers to participation in HIIT after stroke. 6. Facilitators to participation in HIIT after stroke.	1. Demographic information. 2. Opinions on exercise after stroke. 3. Use of HIIT post-stroke. 4. Barriers to recommendation of HIIT after stroke. 5. Facilitators to recommendation of HIIT after stroke.

Abbreviations – HIIT: High Intensity Interval Training.

No identifying information were provided in these questionnaires and datasets were labelled according to the order of record completion to ensure confidentiality. At the completion of the questionnaire, participants were provided an opportunity to complete an expression of interest form to participate in a semi-structured interview. This required participants to provide their email address, residential state within Australia, and preferred day/time to allow the semi-structured interview to be scheduled via Zoom. After completing the questionnaire, the participant was prompted to complete an expression of interest form for the semi-structured interview (if interested) and were directed to a separate REDCap survey to provide their personal information to allow an interview to be organised. Responses of the expression of interest form were not linked to the questionnaire responses to ensure anonymity of the questionnaire.

Semi-structured interview

The scripts of the semi-structured interviews were co-designed with a sport psychologist, with experience in interview conduct and analysis, to ensure the use of appropriate questions to facilitate genuine conversation. The content of the interviews extended upon the questionnaires, and utilised open-ended questions and the use of a 1-10 rating scale to allow the interviewee to lead the conversation. Training interviews were conducted over Zoom between the members of the research team and a qualitative researcher, providing feedback on interview structure and how the session was to be delivered. The interview was

then piloted on one person with stroke and one health professional, with subsequent revisions made to the scripts, including the reordering of questions for people with stroke, and the emphasis placed on the use of aerobic exercise in practice for health professionals.

The final semi-structured interview comprised six questions for people with stroke (Appendix 3) and five questions for health professionals (Appendix 4), along with probing questions to ensure uniformity of all interviews conducted. The concepts of each question in the interview are outlined in Table 4-2. The first few questions explored thoughts on exercise in general after stroke, with the remaining questions focusing specifically on HIIT.

Table 4-2 Concepts covered in the interviews

People with stroke	**Health professionals**
1. Exercise routine after stroke. 2. Importance of exercise using a scale of 1-10, with 1 being not important and 10 being very important. 3. Confidence with exercise using a scale of 1-10, with 1 being not important and 10 being very important. 4. Knowledge of HIIT. 5. Willingness to complete HIIT using a scale of 1-10, with 1 being not important and 10 being very important. 6. Thoughts on the title, High Intensity Interval Training.	1. Work role and experience with people with stroke. 2. Importance of exercise using a scale of 1-10, with 1 being not important and 10 being very important. 3. Experience with HIIT for people with stroke. 4. Willingness to recommend/prescribe HIIT using a scale of 1-10, with 1 being not important and 10 being very important. 5. Thoughts on referral to health professionals for HIIT.

Abbreviations – HIIT: High Intensity Interval Training.

The interviews completed via Zoom were approximately 40 minutes in duration, with consent verbally confirmed at the beginning of the interview. All interviews were recorded on Zoom, with interview transcripts developed in Microsoft Word Online and reviewed by a

member of the research team to ensure accuracy. Alphanumerical identification codes were allocated to each interview participant for use in transcripts, file titles and data dissemination to ensure confidentiality.

4.6.2 Data analysis

Demographic data was tested for normality and presented as mean and standard deviation, frequency and percentage where appropriate. Time post-stroke was calculated as months post-stroke, with the results presented as mean and standard deviation. Questionnaire responses were collated and descriptively analysed by summing the rate of response for each question, presented as frequencies and percentages.

Semi-structured interview data were analysed using the Framework Analysis approach outlined in Table 4-3 (Ritchie & Lewis, 2003) to identify the main themes raised (Hall et al., 2020; Ritchie & Lewis, 2003). The Framework Analysis method is commonly used to analyse semi-structured interviews and is recommended due to the highly structured outputs created to summarise the data collected (Gale et al., 2013).

Two researchers were involved in an inductive, open, and unrestrictive coding process of all transcript data obtained from the interviews conducted. A coding framework was developed to provide a descriptive label to the key matters raised (Gale et al., 2013) and this Framework was implemented across all interviews. The codes allocated referred to substantive things (e.g., behaviours), values (e.g., beliefs that underpin decisions), emotions (e.g., fear) and impressionistic elements (e.g., participant found something difficult to explain) (Gale et al., 2013). The coding framework included themes and sub-themes. Two researchers independently coded all interviews prior to meeting to review coding consistency. Following this meeting, the data was entered into the Framework matrices (i.e., Microsoft Excel document) containing the codes (columns) and the cases (rows) to summarise the data collected from the interviews (Gale et al., 2013). A third independent researcher assisted with any discrepancies.

Table 4-3 Stages in Framework Analysis used for thematic analysis of semi-structured interviews (Ritchie & Lewis, 2003)

Stages in Framework Analysis	**Description of the stage**
1. Familiarisation with the data.	Reading, and re-reading field-notes, transcripts, memos.
2. Identifying a thematic framework.	Researchers jointly developing a set of codes organised into categories to manage and organise the data.
3. Indexing.	Systematically applying the thematic framework to the whole data set.
4. Charting.	Entering data into Framework matrices: spreadsheets containing cells into which summarised data are entered by codes (columns) and cases (rows).
5. Mapping and interpretation.	Interpretive concepts or propositions describing or explaining aspects of the data are the final output of the analysis.

A Synthesised Member Checking approach, according to the developed five-step process (Figure 4-1), was conducted several months after the interviews to ensure the accuracy of the themes identified (Birt et al., 2016). Synthesised Member Checking is a time effective member checking process, allowing participants to read small summaries and provide feedback on the analysed data collected (Birt et al., 2016). Synthesised Member Checking reports were distributed via email.

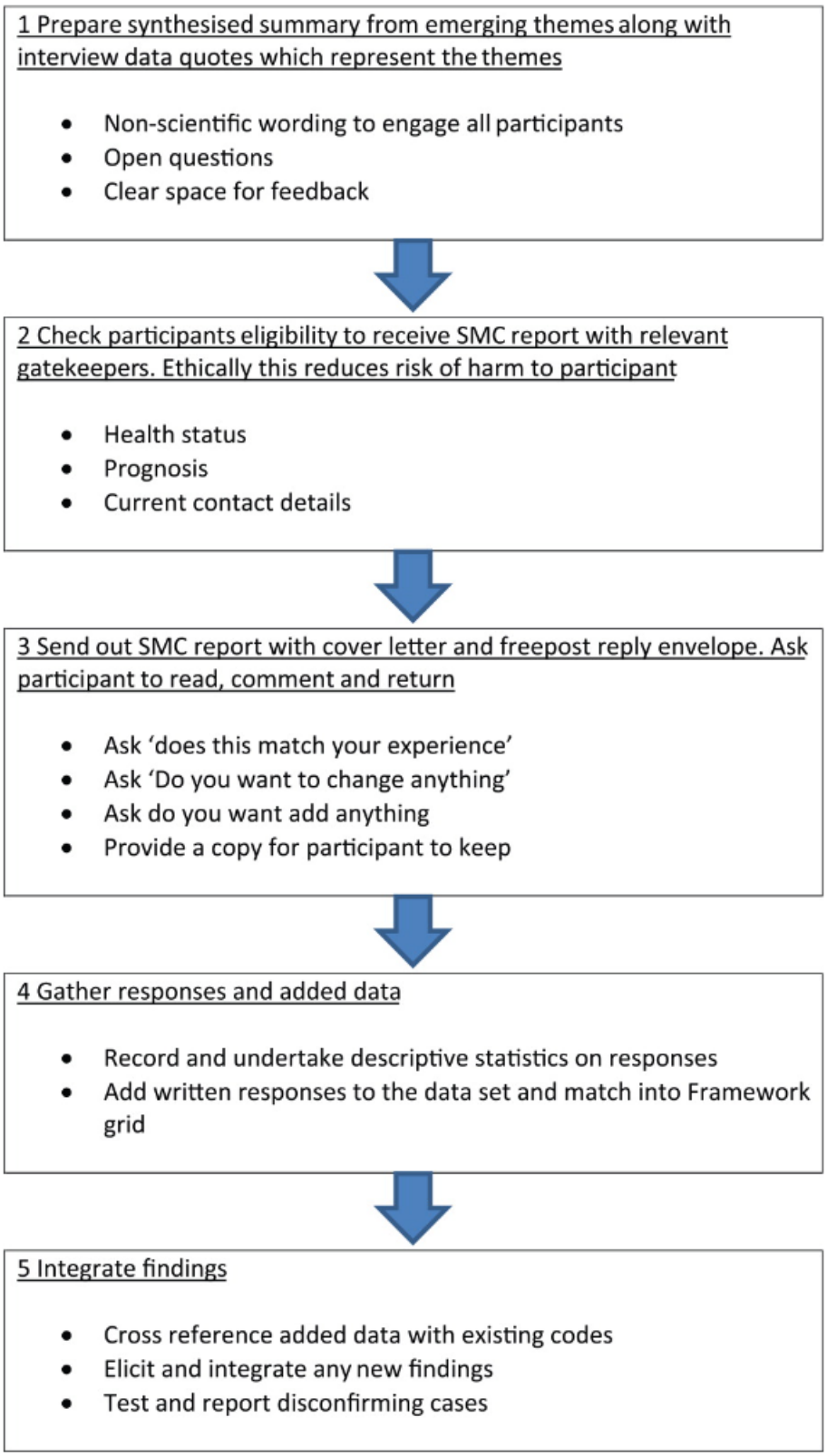


Figure 4-1 Process undertaken in Synthesised Member Checking (Brit et al., 2016)

Abbreviation – SMC: Synthesised Member Checking

4.7 Study 3: Biomarkers for optimising rehabilitation and individualised interventions: BDNF versus lactate

4.7.1 Procedure

Participants in Study 3 underwent a submaximal graded exercise test with venous and fingerprick blood samples collected immediately before and after the completion of the submaximal graded exercise test, and prior to the cool down, to quantify BDNF and lactate concentrations. Participants were asked to not complete planned exercise on the day of the assessment.

Prior to data collection, the candidate and research team underwent formal training in venepuncture to ensure consistency and competency in the data collection methods used.

4.7.1.1 Submaximal graded exercise test

Participants completed a submaximal graded exercise test on an upright cycle ergometer. People with stroke were the originally planned cohort for this study and ethic approval was based on a protocol validated in stroke (Yates et al., 2004). This protocol was modified to suit the healthy participants included in this study recruited due to impacts of the Covid-19 pandemic (protocol provided in Appendix 5). Participants were required to cycle at a comfortable cadence (i.e., between 50 and 70 revolutions per minute (RPM)) with the power output increased every three-minutes by 10 to 20 Watts (resistance on the bike in kiloponds multiplied by the RPM). Standardised verbal encouragement was provided by the exercise physiologist administering the test to assist in the maintenance of the chosen RPM. Peak oxygen uptake (VO_{2peak}) was calculated using the American College of Sport Medicine (ACSM) cycle ergometer VO2 metabolic equation (Liguori et al, 2021). VO_{peak} is reported in millilitres per kilogram per minute ($VO_2.mL^{-1}.kg^{-1}.min^{-1}$).

The test was terminated when the participant reached any of the following criteria (Yates et al., 2004):

- Participant reached 90% of age-predicted heart rate (220 minus participant age) or 18/20 Rating of Perceived Exertion (RPE) (Borg, 1970).
- Participant-reported angina, dyspnoea and/or fatigue.

- Voluntary cessation (for any reason).
- Inability to maintain the specified cycling cadence.
- Oxygen saturation <85%.

4.7.1.2 Blood collection

Preparation and training

All members of the research team completed the online ICH Good Clinical Practice E6 (R2) course (https://globalhealthtrainingcentre.tghn.org/ich-good-clinical-practice/). This short course outlines the international ethics and scientific quality for designing, conducting, recording, and reporting trial information, establishing unified standards to increase the acceptability of the information presented (ICH, 2022).

The research candidate and another member of the research team completed an Introduction to Venepuncture and Cannulation course through the Australian Healthcare Academy in 2022 and subsequent real-world practice. This course comprised theoretical and practical components covering anatomy and physiology, clinician, and client safety as well as standards of practice for blood collection. A one-day practical training course was completed, where the members of the research team involved in blood collection were required to practice venepuncture and cannulation on a model arm, with assessment prior to being awarded the course completion. The venepuncture protocol was practiced by members of the research team prior to the commencement of the study to ensure competence and safety.

Existing Standards of Practice for blood collection and analysis in the in the biochemistry laboratory at ACU, Strathfield were modified in accordance with the specific models (i.e., centrifuge) used and in accordance with World Health Organisation and Department of Health guidelines, and product manuals.

BDNF concentration

Blood samples were collected from median cubital vein using a butterfly needle (Livingstone BD Vacutainer safety-lok blood collection set, with luer adapter, 21-gauge x 0.75-inch needle, 12 inches tubing). Blood was collected into 8.5 mL Clot Activator and Serum separating Gel tubes (Livingston, Mascot, NSW) immediately prior to and post submaximal graded exercise test (prior to cool down). After 20 to 30-minute coagulation time at room temperature, samples were centrifuged at 4000 RPM for 10-minutes at room temperature, and serum stored in 0.5 millilitre (mL) aliquots at -20 degrees Celsius, within a purpose-built refrigerator in the biochemistry laboratory at ACU Strathfield campus, until analysis. Serum BDNF was assayed using ELISA using a commercial kit (ab212166-Human BDNF, Abcam, Cambridge, MA) following manufacturer's instructions. Absorbance was measured at 450 nanometres (xMark microplate absorbance reader, BIO-RAD, Cat. 168-1150, Hercules, CA, USA) immediately after a stop solution was added. All samples from a given participant were analysed in duplicate, on the same plate, and all samples were analysed on the same day. ELISA kit sensitivity was 15.6-1000 picograms per millilitre (pg/ml) with an intra-assay coefficient of variation reported by the manufacturer as 2.8% and inter-assay coefficient of variation of 5.3%.

BDNF genotype

BDNF genotype testing was completed by the Royal Prince Alfred Hospital Department of Chemical Pathology due to limited resources available at ACU Strathfield Campus. DNA was extracted using QIAGEN® QIAcubeTM automated DNA extraction with elution in Invitrogen TE buffer REF 12090-015. A total of 2-3 extractions were completed per blood tube.

TaqMan Genotyping for detection of *BDNF* c.196G>A (rs6265 or Val66Met polymorphism)

The *BDNF* SNP c.196G>A was detected by a TaqMan genotyping probe assay using the QuantStudio™ 3 System. The Polymerase Chain Reaction (PCR) reaction mixture contained 2X Genotyping Mastermix REF4371355 (Applied Biosystems) (6.25 microlitre (µL)/reaction), ultra-pure water (3.5 µL per reaction), 20X genotyping assay probe specific for *BDNF* c.196G>A (probe REF 4351379, Assay ID C_11592758_10) of 0.25 µL per reaction and DNA of approximately 50 nanogram per reaction. Thermal cycling conditions were as follows; 1 cycle of pre-hold reading (60 degrees Celsius, 30 seconds), Amplitaq gold enzyme activation;

1 cycle 90 degrees Celsius 10 minutes, 40 cycles of PCR; 90 degrees Celsius 15 seconds, 60 degrees Celsius 1 minute and lastly one cycle of post hold reading 60 degrees Celsius 30 seconds. DNA samples from participants with confirmed variant and wild type sequences at *BDNF* codon 196 were used as controls for TaqMan genotyping. Genotyping was repeated on a separate DNA extraction from each blood sample to confirm results.

Sanger sequencing confirmation of *BDNF* c.196G>A (rs6265 or Val66Met polymorphism)

To confirm the accuracy of the TaqMan Genotyping method, 5 DNA samples (4 normal and 1 heterozygous for *BDNF* c.196G>A) were tested by Sanger Sequencing using the AB 3730xl gene analyser. PCR to amplify the region flanking *BDNF* c.196 was performed using primers *BDNF*-F1 forward 5' CCTACAGTTCCACCAGGTGAGAAGAGTG 3' and *BDNF*-R1 reverse 5' TCATGGACATGTTTGCAGCATCTAGGTA 3' (2 µL of 10 millimolar mass (mM) primer per reaction), and Invitrogen Platinum® PCR Super Mix High Fidelity polymerase (45 µL per reaction). PCR products were purified with ExoSAP IT enzyme as per manufacturer instructions and cycle sequencing reaction was completed with BigDye Terminator ® V3.1 as per manufacturer instructions. XTerminator premix was used to purify products from the sequencing reaction. The sequencing reactions were run on the AB 3730xl gene analyser (Applied Biosystems). Sequences were compared to *BDNF* reference sequence NG_011794.1 using Mutation Surveyor V5.1.2 (SoftGenetics).

Lactate concentration

A fingerprick blood sample was obtained from the distal part of the finger of the participant using a lancet (Unistik 3, 21G 2.0 millimetre (mm), Malaysia). The collected blood sample was immediately placed on the lactate test strip and inserted into the Lactate Pro 2 Analyser (LP2: Arkray, Kyota, Japan), a hand-held battery-operated analyser. The Lactate Pro 2 Analyser requires a small blood sample, short time for analysis (Crotty et al., 2021) and is a reliable portable device for calculating blood lactate (Bonaventura et al., 2015). Blood lactate concentration was calculated in accordance with the Lactate Pro 2 Analyser established protocol (Laktate, 2013), whereby the blood sample is analysed using an enzymatic amperometric detection method (Bonaventura et al., 2015). The reaction between blood lactate and the enzyme lactate oxidase on the inserted sensor produces a

voltage signal which directly corresponds to the lactate concentration of the sample (Bonaventura et al., 2015).

4.7.2 Data analysis

Demographic data was tested for normality and presented as mean and standard deviation, frequency and percentage where appropriate. If not normal, data were presented as median and interquartile range. Nonparametric assessment data was logarithmically transformed. BDNF concentration was presented as mean and standard deviation at each timepoint in the value nanograms per millilitre (ng/mL). BDNF genotype with the wild type nucleotide G in position 196 (c.196G) were reported as "without the Val66Met polymorphism. Samples that were heterozygous c.196G>A or homozygous c.196G>A were reported as "with the Val66Met polymorphism". Lactate concentration was presented as mean and standard deviation at each timepoint in the value millimoles per litre (mmol/L). Post-exercise concentration minus pre-exercise concentration was used to quantify the change in BDNF and lactate concentration. The significance of the change in concentration was calculated using a Two-Sided Paired Samples T-Test. Correlational analyses were undertaken using parametric (Pearson) or nonparametric (Spearman) analyses if assumptions were violated to examine the correlation between BDNF and lactate concentrations. Significance was taken at $p<0.05$.

4.8 Study 4: Relationship between the Motor Activity Log and the Rating of Everyday Arm-Use in the Community and Home in an Australian post-stroke population

4.8.1 Procedure

Participants completed a two-week intensive upper limb therapy program at the Exercise Lifestyle Clinic, NSW or the Banyo Health Clinic, Queensland. There is a weak recommendation for the use of a CIMT program (Stroke Foundation, 2022), while the barriers to application (i.e., long durations of therapy, increased labour for clinicians and clients) may diminish its feasibility in a clinical setting (Abdullahi, 2018; Fleet et al., 2014; Page et al., 2004). Therefore, a two-week intensive upper limb therapy program was provided to facilitate improvements in motor control and functional outcomes of the paretic

limb after stroke (Shi et al., 2011; Smania et al., 2012) in a shorter period than CIMT (Lee et al., 2019). The two-week upper limb therapy program delivered at the participating sites followed key principles of CIMT: (1) intensive practice of the paretic upper limb, (2) training by shaping, (3) constraint of the non-paretic limb, and (4) home practice (Taub et al., 2006; Taub et al., 2013). Exercises were individualised to the participant's motor function (Taub et al., 2006) with increasing task complexity, strength, and speed, as tolerated.

Exercise Lifestyle Clinic, Strathfield

Participants completed a two-week intensive upper limb therapy program delivered by an accredited exercise physiologist trained in mCIMT delivery. The program consisted of one-hour of time-on-task supervised task-oriented training on ten consecutive weekdays, augmented by progressively increasing home practice. Home practice commenced with 15-minutes on day two of the program and increased by 15-minutes until 180-minutes was achieved by day 10 (McNulty et al., 2015). Participants were required to wear a mitt on the non-paretic upper limb during supervised sessions and for up to 90% of waking hours, as part of the behavioural contract developed with the accredited exercise physiologist (Taub et al., 2006). The mitt was removed for ambulation, toileting and other activities deemed unsafe to be completed single-handed through communication with the accredited exercise physiologist. The CIMT transfer package is a set of behavioural interventions that aimed to promote the transfer of clinic gains to daily function, including a behavioural contract and daily completion of the MALQOM to promote safety and monitor adherence to home practice, paretic upper limb use and mitt compliance during mCIMT, and to provide an opportunity for goal setting and problem solving (Taub et al., 1993; Wolf et al., 2006).

Banyo Health Clinic, Brisbane

Participants completed a two-week intensive upper limb therapy program delivered by fourth-year occupational therapy students under the supervision of a registered occupational therapist Professional Practice Educator. The program consisted of four-hours of supervised task-oriented training on ten consecutive weekdays, augmented by 30-minutes of home practice daily. Adherence to home practice was not monitored and no transfer package was administered in this program. Participants were required to wear a mitt on the non-paretic upper limb during supervised sessions and for 20-minutes per night

during on weekdays and as tolerated on one day of the weekend. Participant were required not to wear the mitt on one day per week.

While the upper limb therapy program provided differed between the two study sites, this study explored the relationship between the MAL-30 and the REACH, not the effect of the intervention on paretic upper limb use.

4.8.2 Outcome measures

Participants completed the MAL-30 (i.e., MALAOU and MALQOM) and REACH at baseline and following completion of the two-week intensive upper limb therapy program.

Motor Activity Log-30

The MAL-30 is a 30-item scale used to assess the amount of use and the quality of movement of the paretic upper limb, as self-reported by the person with stroke (Uswatte et al., 2006). The MAL consists of two separate scales to report on these outcomes, the MALAOU and the MALQOM, respectively. The 30-items examined include a range of personal care activities and ADLs, such as 'washing your hands' and 'use a TV remote control' (Uswatte et al., 2006). All items on each scale are scored using a six-point ordinal scale (i.e., zero to five), with a higher score on the respective subscale indicating a greater amount and quality of use (Uswatte et al., 2006). The results of the 30-item scale are reported as the average score, which is calculated by dividing the total score by the number of items that were considered possible to complete with the paretic limb. Items considered impossible to perform by the participant (e.g., if unable to write with the paretic limb as this is not the hand they write with or the participant had no hair) were excluded and the average was calculated using the remaining items (e.g., divide sum by 29 and not 30) (Taub et al., 2011).

Rating of Everyday Arm-use in the Community and Home

The REACH comprises two separate scales to classify paretic upper limb, and considers hand dominance (Obembe et al., 2023; Simpson et al., 2013). Hand dominance is important to consider as it can impact paretic limb use after stroke (Haaland et al., 2012). Therefore, the

REACH aims to account for variation limb use according to the dominance of the paretic limb.

The REACH classifies upper limb function across six categories, from 'no use' (i.e., level 0) to 'full use' (i.e., level 5) (Simpson et al., 2013). As the REACH is a self-reported measure, an algorithm and checklist is used to classify paretic limb use. The algorithm is used to narrow down the participant's functional level, with the level to be confirmed by the checklist (Obembe et al., 2013; Simpson et al., 2013). For example, a participant is asked a 'yes' or 'no' question regarding their use of the limb in question and prompted to a potential classification level based upon the response provided. The checklist expands upon the function of the paretic limb expected for that classification, and if this is correct for the individual, the level is awarded. Alternatively, the level above or below is checked and awarded if appropriate (Simpson et al., 2013).

4.8.3 Data analysis

Demographic data was tested for normality and presented as mean and standard deviation, frequencies, and percentages where appropriate. If not normal, data were presented as median and interquartile range. MALAOU and MALQOM results were presented as mean and standard deviation at each timepoint. Nonparametric assessment data was logarithmically transformed. REACH classification results were presented as mean and standard deviation at each timepoint (i.e., before and after upper limb therapy). The significance of the change in scores were calculated using a Two-Sided Paired Samples T-Test. Spearman rank correlation coefficient (rho) was used to examine the correlation between the MALAOU, MALQOM, and REACH scores. Significance was taken at $p<0.05$.

4.9 Ethical approvals and considerations

4.9.1 Ethical approvals

Two separate ethical approval processes were undertaken within this program of research. The processes by which these were obtained are outlined below.

Ethical approval for Study 2

The mixed methods study required ethical approval from the ACU Human Research Ethics Committee (HREC). The research candidate completed the ethical application process via the ACU research database, ORION. As part of the ACU HREC approval process, all research must be peer-reviewed. This study protocol was peer-reviewed by the research candidate's confirmation of candidature panel. Ethical approval for the mixed methods study was granted by the ACU HREC on 20th February 2023 (2022-2702H) (Appendix 6).

Ethical approval for Study 3 and 4

Royal Prince Alfred HREC was the primary ethical approval site for Study 3 and 4. Site specific governance was then sought from Royal Rehab Research Governance Office (research governance office for Royal Rehab Private Petersham) due to recruitment through this facility, and ACU HREC as the studies were run on ACU campuses.

The research candidate completed the primary ethical application process via REGIS (Research Ethics Governance Information System), a database for all NSW government health facilities. Ethical approval was obtained on 11th May 2021 (X21-0432) (Appendix 7). Site specific governance was then obtained from Royal Rehab Research Governance Office. Ethics approval was sought via email correspondence with the Royal Rehab Director of Research and the Royal Rehab Private Petersham General Manager. Ethics approval was obtained on 25th June 2021 (2021-ETH12179) (Appendix 8). Site specific governance was then obtained from ACU HREC. Ethics approval was sought via ORION and obtained on 19th May 2021 (2022-2698RC) (Appendix 9).

4.9.2 Ethical considerations

Numerous ethical considerations were required within the development and execution of Study 2, 3 and 4 within this program of research. These will be outlined below.

Screening and consent

For Study 2, e-Consent was obtained prior to screening and completion of the online questionnaire. The individual was provided with the participant information statement on REDCap, which could also be downloaded to keep in their personal records. Prior to

completing the questionnaire in REDCap, participants were required to complete a series of questions to ensure eligibility for the study (i.e., 'yes' or 'no' questions relating to the inclusion criteria). If eligible based on the responses provided, the participant was required to provide e-Consent. Once e-Consent was provided the participant was directed to start the questionnaire. If the individual was not eligible for this study (i.e., answered 'no' to an eligibility criteria) the individual was unable to proceed to the questionnaire, with a message on screen outlining they do not meet the inclusion criteria and cannot participate. All steps were automated by the REDCap platform, as designed by the research candidate. The process was tested by members of the research team and at least one lived expert prior to release and distribution.

For Study 3 and 4, eligible individuals were screened against the inclusion criteria by a member of the research team. Individuals were provided time to read the participant information statement and discuss the study with any family, friends, or other health professionals they choose. Members of the research team were also available via telephone or face-to-face to answer questions. If interested in participating in the study, the individual was asked to sign the participant consent form in the presence of a member of the research team. Participants were made aware that participation in the study was voluntary, and they could withdraw from the study at any time without consequence or impact on their usual care rehabilitation.

Data and specimen storage

For Study 2, all questionnaire responses were anonymous, with no identifying details provided by the participant. Interview expression of interest forms included personal information; however, this was kept separate from all questionnaire data. REDCap responses were downloaded and analysed in SPSS (IMB SPSS Statistics, version 29.0.1.0). Audio-visual recordings of the interviews were downloaded from Zoom and transcribed using Microsoft Word Online. Each participant was provided an alphanumerical code, and all identifying information was removed (e.g., name, place of work). All data files were saved to the ACU OneDrive of the research candidate, which is password protected in accordance with ACU data management policies.

At the commencement of Study 3 and 4, all participants were allocated a unique alphanumeric code, which was used instead of their names for all data collection and analysis purposes. Participant initials and the corresponding alphanumeric codes was recorded in the master code sheet stored on the ACU OneDrive of the research candidate, which is password protected. All hard copy data collection sheets (Study 3 and 4) and blood collection tubes (Study 3 only) were labelled using the participant alphanumerical code to ensure confidentiality. Data was transcribed into REDCap using the participant alphanumerical code and will be kept for up to 15 years post-publication in accordance with Royal Prince Alfred Hospital HREC and ACU HREC guidelines. Blood collection tubes were stored within the biochemistry laboratory at ACU Strathfield campus or the Department of Chemical Pathology laboratory at Royal Prince Alfred Hospital for analysis. Used samples were destroyed in accordance with the biohazardous waste protocols at the respective locations. Remaining blood samples will be stored for 15 years in accordance with Royal Prince Alfred Hospital HREC and ACU Ethics guidelines.

Chapter 5 STUDY 1: EFFECT OF EXERCISE ON BRAIN-DERIVED NEUROTROPHIC FACTOR IN STROKE SURVIVORS: A SYSTEMATIC REVIEW AND META-ANALYSIS

5.1 Preface

No systematic review and/or meta-analysis has examined the effect of exercise training parameters on BDNF concentration post-stroke. Most knowledge extends from reviews of general neurological populations (Mackay et al., 2017) or grouped interventions (Mojtabavi et al., 2022). A systematic review and meta-analysis presenting data for specific training parameters (i.e., aerobic versus non-aerobic, duration of aerobic exercise, intensity of aerobic exercise) was needed to further understand the effect of exercise training parameters on BDNF concentration after stroke. This was necessary to inform subsequent studies in this program of research which were planned to investigate the impact of aerobic exercise on BDNF concentration in post-stroke participants. The results of this systematic review and meta-analysis were anticipated to inform the exercise intervention proposed for Study 5 (Chapter 9).

The systematic review and meta-analysis presented in this chapter is published in Stroke.

This chapter is an extended version of the following publication;

Ashcroft, S. K., Ironside, D. D., Johnson, L., Kuys, S. S., & Thompson-Butel, A. G. (2022). Effect of exercise on brain-derived neurotrophic factor in stroke survivors: A systematic review and meta-analysis. *Stroke (1970)*, *53*(12), 3706–3716. https://doi.org/10.1161/STROKEAHA.122.039919

5.2 Abstract

Objective. To identify the intensity and duration of exercise required to increase BDNF concentration post-stroke.

Methods. A systematic search of seven electronic databases were searched from inception until January 31st, 2022. Retrieved articles which conducted experimental or observational studies of people post-stroke who completed a prescribed exercise intervention with changes in BDNF concentration as an outcome measure were eligible for inclusion. The Revised Cochrane Risk-of-Bias Tool for Randomised Interventions (RoB 2) and the Risk of Bias in Non-Randomised Studies – of Interventions (ROBINS-I) were used to assess the methodological quality of the included randomised and non-randomised trials, respectively. Data were extracted from the included studies including study, participant, intervention, and outcome characteristics. A meta-analysis was completed based on the assessment of the included studies against a predetermined set of criteria.

Results. Database searches yielded 2,195 articles. Seventeen studies (six randomised trials) including a total of 687 participants met the eligibility criteria and were included for meta-analysis. Significant improvements were observed in BDNF concentration following a single session of high intensity aerobic exercise (mean difference [MD] 2.49 ng/mL, 95% CI 1.10 to 3.88), a program of high intensity aerobic exercise (MD 3.42 ng/mL, 95% CI 1.92 to 4.92).

Conclusions. Significant improvements were observed in BDNF concentration following a single session of high intensity aerobic exercise (mean difference [MD] 2.49 ng/mL, 95% CI 1.10 to 3.88), a program of high intensity aerobic exercise (MD 3.42 ng/mL, 95% CI 1.92 to 4.92). High intensity aerobic exercise and a program of non-aerobic exercise can increase circulating BDNF concentrations, which may contribute to increased neuroplasticity.

Registration. URL: https://www.crd.york.ac.uk/PROSPERO/; Unique identifier: CRD42021251083

5.3 Introduction

Stroke is a leading cause of acquired disability (MacLellan et al., 2011), ranked as the third leading cause of death and mortality combined worldwide (Stark et al., 2021). Stroke survivors experience impaired movement, cognition, speech, and function (Molle Da Costa et al., 2019). Altered functional capacity often results in increased sedentary behaviour and

reduced physical fitness compared to healthy populations (Ploughman & Kelly, 2016). Multidisciplinary rehabilitation, including aerobic exercise, is recommended to optimise recovery and functional improvements following stroke (Cassidy & Cramer, 2017). Aerobic exercise aids motor learning, and relearning (Quaney et al., 2009), and is mediated by neuroplasticity.

BDNF is a biomarker of neuroplasticity of interest post-stroke due to its association with stroke prognosis and recovery (Schabitz et al., 2007). BDNF, produced and secreted within the central and peripheral nervous system (Yilmazer et al., 2019), is closely associated with energy metabolism and the maintenance of homeostasis due to its upregulation in response to changes in energy metabolism within the body (Marosi & Mattson, 2013). BDNF is released in an activity-dependent manner, with greater concentrations of circulating BDNF demonstrated following exercise (Knaepen et al., 2010). Most evidence supporting the mechanisms involved in exercise induced BDNF increases arises from animal models (Ploughman & Kelly, 2016). Though promising results have also been demonstrated in healthy adults (Knaepen et al., 2010).

There is little systematic evidence reporting the effects of exercise on BDNF concentration in stroke survivors. A meta-analysis by Mackay et al. (2017) demonstrated a program (i.e., 20.6 ± 20 hours) of aerobic exercise increased BDNF concentration, but only one of the included studies examined stroke survivors, and non-aerobic exercise interventions were excluded. While Mojtabavi et al. (2022) demonstrated acute effects of physical training (e.g., regular physiotherapy, aerobic exercise) on BDNF concentration, it remains unknown how exercise training parameters, such as modality and intensity of exercise, influence BDNF concentration in people with stroke. There is currently no systematic review demonstrating the effects of resistance training on BDNF concentration post-stroke, and resistance training studies have produced variable results in healthy adults (Levinger et al., 2008; Yarrow et al., 2008).

Pre-clinical findings suggest the exercise stimulus provided must achieve an appropriate intensity to increase BDNF concentration (Ploughman & Kelly, 2016). Moderate to high intensity aerobic exercise have been found to increase BDNF concentration in rat models of

stroke (Ploughman & Kelly, 2016), but whether this, or other forms of exercise training, (i.e., resistance training), similarly increase BDNF in humans is unclear. Given the potential link between exercise, increased concentration of circulating BDNF and improved stroke recovery (Liu et al., 2020), a clearer understanding of the optimal exercise prescription to increase BDNF concentration is necessary. This systematic review and meta-analysis aims to identify the intensity and duration of exercise required to produce increases in blood-derived BDNF concentration post-stroke.

5.4 Methods

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021) and is registered with International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021251083).

5.4.1 Literature search

The APA Thesaurus of Psychological Index Terms, CINAHL, Embase Classic + Embase, Medline, PubMed, SportDiscus and Web of Science Core Collection electronic databases were systematically searched from inception until January 31st, 2022. The following umbrella search terms were used in each database, along with database-specific subject headings: *stroke (e.g., cerebrovascular event, haemorrhage, ischaemic), exercise (e.g., aerobic, strength, balance), brain-derived neurotrophic factor (e.g., BDNF, neurotrophic factor)*. Full search strategies are found in Supplementary Material 1. Reference lists of included studies were screened for relevant studies. English language restrictions were imposed during searches.

5.4.2 Eligibility criteria

Retrieved searches were downloaded from each database and imported into EndNote (https://endnote.com/). Duplicates were manually removed before the retrieved searches were uploaded to Covidence. All screening was completed using Covidence (https://www.covidence.org/). Title and abstract of the retrieved searches were screened by two reviewers (SKA and DDI) independently. Full-text articles were obtained and included for full-text screening based on the following inclusion criteria: (1) human study (≥18 years),

(2) diagnosis of stroke, (3) investigating the effects of an exercise program of any modality (e.g., aerobic, resistance, balance/proprioception, etc.), (4) measurement of blood-derived BDNF concentration and (5) experimental or observational study. Articles were excluded from the review if they were (1) review studies, (2) trial registrations, (3) conference abstracts, (4) protocol papers or (5) duplicate papers. Disagreements between reviewers were moderated by a third independent assessor (ATB) until consensus was reached.

5.4.3 Methodological quality assessment

Two assessment tools were used to appraise the methodological quality and risk of bias in the included studies. To assess the risk of bias of included randomised trials, the Revised Cochrane Risk-of-Bias Tool for Randomised Interventions (RoB 2) (Sterne et al., 2019) was used. To assess the risk of bias of included non-randomised trials, the Risk of Bias in Non-Randomised Studies – of Interventions (ROBINS-I) (Sterne et al., 2016) was used. The RoB 2 has demonstrated moderate inter-rater reliability and undetermined validity (Minozzi et al., 2020), while the ROBINS-I has demonstrated moderate criterion validity and substantial inter-rater reliability (Zhang et al., 2021). The RoB 2 and ROBINS-I both encompass a fixed set of domains to cover all aspects of a trial that may lead to risk of bias, with signalling questions to assist in analysis (Boutron et al., 2021). The risk of bias is calculated for each domain and an overall risk of bias is assessed for the entire study. Two independent assessors implemented these criteria (SKA and DDI), with disagreements between assessors moderated by a third independent assessor (ATB). The GRADE approach (Brozek et al., 2009) to identify the certainty of evidence was completed by one independent assessor (SKA) and reviewed by the remaining authors.

5.4.4 Data extraction and synthesis

A standardised electronic data extraction form was developed using Microsoft Excel (Microsoft Pty Ltd) to obtain all necessary information relevant to this review. Extraction was completed by a single reviewer (SKA) and a second reviewer (DDI) validated the information. Extracted study data included: study characteristics (i.e., study type, year of publication), participant characteristics (i.e., stroke type, stroke severity, time post-stroke, age, sex), sample size, characteristics of the exercise intervention (i.e., frequency, intensity,

duration of each session, modality, duration of the intervention), characteristics of the comparison group (if applicable) and outcome measures, including BDNF analysis methods and BDNF concentration values. Missing data were sought from study authors via email. If no response was received despite follow up, the missing information was described as not reported.

Participant information was collated and mean ± standard deviation (SD) (e.g., age, time post-stroke) or frequency (percentage) (e.g., stroke diagnosis) was determined. Frequency, intensity, time, type, and duration of the intervention were extracted for each intervention within the included studies. The intensity of the exercise intervention provided was categorised as 'low', 'moderate' and 'high' intensity as outlined by the ACSM (Pescatello, 2014) to allow for ease of comparison and uniformity with previous literature (Ploughman & Kelly, 2016) (Table 5-1). Blood-derived BDNF concentrations were converted to ng/mL (e.g., divide by 1000 to convert pg/mL to ng/mL) if not originally reported in this unit of measurement.

Table 5-1 ACSM aerobic exercise intensity classifications (Pescatello et al., 2014)

Aerobic exercise intensity classification	Heart rate maximum	Heart rate reserve	Maximal oxygen uptake	Rating of perceived exertion
Low	57-<64% HR_{max}	30-<40% HRR	37-<45% VO_{2max}	9-11/20 RPE
Moderate	64-<76% HR_{max}	40-<60% HRR	45-<64% VO_{2max}	12-13/20 RPE
High	76-<96% HR_{max}	60-<90% HRR	64-<91% VO_{2max}	14-17/20 RPE

Abbreviations – HR_{max}: Heart rate maximum; HRR: Heart rate reserve; VO_2max: Maximal oxygen uptake; RPE: Rating of perceived exertion (Borg, 1970).

5.4.5 Meta-analysis

A meta-analysis was planned based on the following criteria: (1) included studies were clinically homogenous, (2) included studies were statistically homogenous determined using

a Chi squared test (I^2), and (3) relevant data were reported amongst the group of homogenous studies to allow for comparison (i.e., mean and SD). A fixed-effects model was used for studies determined to be highly homogenous (I^2 <60%) (McKenzie et al., 2021). A random-effects model was used for studies considered highly heterogenous (I^2 ≥60%) (McKenzie et al., 2021). Meta-analysis results were reported as mean differences (MD) and 95% confidence intervals (CI) within the results of the meta-analysis. The effect size was reported using a Z score and the effect was described in accordance with established cut-offs (Zlowodzki et al., 2007). All meta-data analyses were conducted using the Cochrane Review Manager software, RevMan version. 5.4. (http://ims.cochrane.org/revman/download).

5.5 Results

5.5.1 Included studies

The literature search yielded a total of 2,195 articles, of which 1,489 were screened for eligibility after 706 duplicates were manually removed (Figure 5-1). A total of 1,446 articles were excluded following title and abstract screening. The remaining 43 articles met the eligibility criteria, and their full text were retrieved for screening. Twelve additional articles were added to the full-text screening following a hand search of included studies reference lists. Following full-text screening, 37 studies were excluded as they did not satisfy the inclusion criteria of this review. Thus 17 studies were included for analysis (Figure 5-1) (Boyne et al., 2020; Chang et al., 2018; Charalambous et al., 2018; Chaturvedi et al., 2020; de Morais et al., 2018; Du et al., 2021; El-Tamawy et al., 2014; Harnish et al., 2018; Hsu et al., 2021; Kim et al., 2019; King et al., 2019; Koroleva et al., 2020; Mackay et al., 2021; Ploughman et al., 2019; Rahayu et al., 2020; Ryan et al., 2019; Valkenborghs et al., 2019).

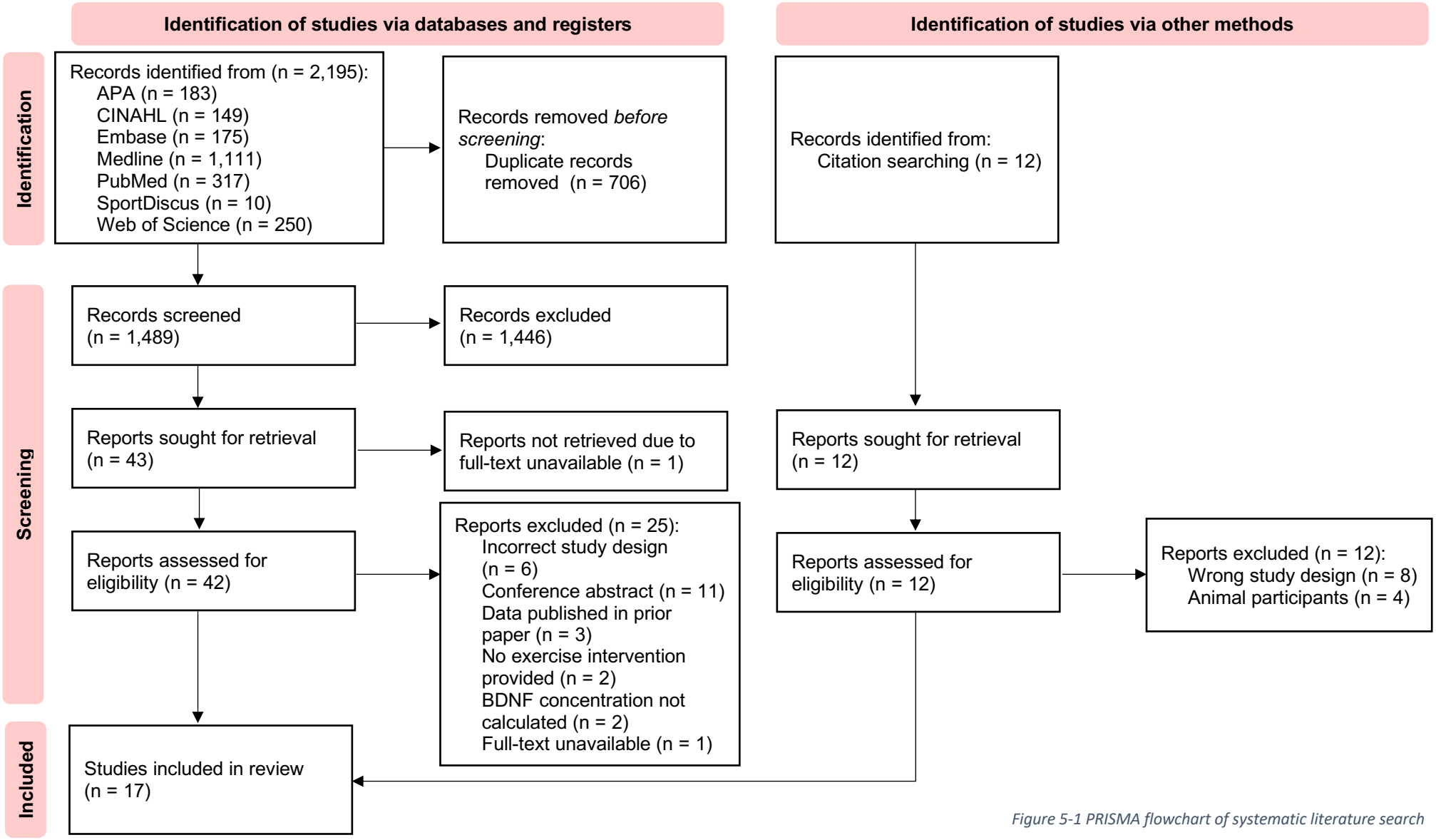


Figure 5-1 PRISMA flowchart of systematic literature search

Of 17 studies included, one was published in 2014 (El-Tamawy et al., 2014) and the remaining 16 studies were published between 2018 and 2021. Six (35%) of the included studies were randomised trials (including four randomised controlled trials) (Du et al., 2021; Hsu et al., 2021; Kim et al., 2019; Ploughman et al., 2019; Rahayu et al., 2020; Valkenborghs et al., 2019), one (6%) was a pseudo-randomised trial (Mackay et al., 2021), and the remaining ten (59%) were non-randomised studies (Boyne et al., 2020; Chang et al., 2018; Charalambous et al., 2018; Chaturvedi et al., 2020; de Morais et al., 2018; El-Tamawy et al., 2014; Harnish et al., 2018; King et al., 2019; Koroleva et al., 2020; Ryan et al., 2019).

A total of 687 participants were included across the 17 studies, 418 (61%) males and 259 (38%) females (Table 5-2). Participant sex was not reported in one intervention group in one study (n = 10, 1% of total included participants) (Ryan et al., 2019). Five (29%) of the studies included participants with ischaemic stroke only (de Morais et al., 2018; Du et al., 2021; El-Tamawy et al., 2014; Koroleva et al., 2020; Rahayu et al., 2020) and the remaining twelve (71%) included participants following ischaemic or haemorrhagic stroke. Mean ± SD age of the included participants was 58 ± 5 years (range, 28-81 years). One of the included studies reported only the age range of included participants (43-81 years) (Ryan et al., 2019).

Of the 17 included studies, four (24%) targeted acute (1-7 days) stroke (Chang et al., 2018; Chaturvedi et al., 2020; Koroleva et al., 2020; Rahayu et al., 2020) and five (29%) targeted chronic (>6 months) stroke (Boyne et al., 2020; Charalambous et al., 2018; Harnish et al., 2018; Mackay et al., 2021; Ryan et al., 2019), with the remaining eight studies (47%) including people across the spectrum of time post-stroke. Mean ± SD time post-stroke of the participants in the included studies was 47 ± 36 months (range, 24 hours – 9.2 years). Four studies reported only the range of time post-stroke (0-15 days (Chaturvedi et al., 2020), 3-18 months (El-Tamawy et al., 2014), >2 years (Hsu et al., 2021) and 0-90 days (Koroleva et al., 2020)). Stroke severity, as assessed using the National Institutes of Health Stroke Scale (NIHSS) was reported in four (23%) of the included studies (Chang et al., 2018; Chaturvedi et al., 2020; King et al., 2019; Ploughman et al., 2019), with a mean ± SD score of 5.2 ± 1.3 (max. 42, with higher scores indicating greater symptom severity).

Outcomes and Provided Interventions

All included studies provided exercise interventions and examined the change of blood-derived BDNF concentration at various timepoints during the study (Table 5-3). Within the 17 included studies, a total of 37 exercise interventions were utilised. All studies reporting single session interventions utilised a single modality, while studies reporting a program of exercise utilised single and combined interventions.

Table 5-2 Characteristics of participants in the included studies

Study	Country of study	Study type	Stroke type	Stroke severity (NIHSS) (mean ± SD)	Number of participants (number of females)	Time post-stroke (mean ± SD)	Age (years) (mean ± SD)
Boyne et al., 2020	USA	Cohort study	Ischaemic or Haemorrhagic	NR	16 (7)	6.5 ± 4.1 years	57.4 ± 9.7
Chang et al., 2018	Korea	Cohort study	Ischaemic or Haemorrhagic	7.5 ± 5.4	38 (15)	15.8 ± 6 days	62.9 ± 14.6
Charalambous et al., 2018	USA	Cohort study	Ischaemic or Haemorrhagic	NR	37 (14)	67.9 ± 60.4 months	58.0 ± 12.0
Chaturvedi et al., 2020	India	Prospective cohort study	Ischaemic or Haemorrhagic	Mild (1-4): n = 17 Moderate (5-14): n = 60 Severe (15-25): n = 7	208 (82)	0-15 days	55.3 ± 11.1
de Morais et al., 2018	Brazil	Cohort study	Ischaemic	NR	10 (5)	9.2 ± 5.8 years	58 ± 12.8
Du et al., 2021	China	Randomised trial	Ischaemic	NR	24 (10)	44.4 ± 4.0 days	47.8 ± 4.8

Study	Country of study	Study type	Stroke type	Stroke severity (NIHSS) (mean ± SD)	Number of participants (number of females)	Time post-stroke (mean ± SD)	Age (years) (mean ± SD)
El-Tamawy et al., 2014	Egypt	Cohort study	Ischaemic	NR	30 (9)	3-18 months	48.4 ± 6.4
Harnish et al., 2018	USA	Cohort study	Ischaemic or Haemorrhagic	NR	12 (5)	4.7 ± 3.3 years	57.9 ± 14.4
Hsu et al., 2021	Taiwan	RCT	Ischaemic or Haemorrhagic	NR	23 (3)	>2 years	55.8 ± 3.82
Kim et al., 2019	Korea	Randomised trial	Ischaemic or Haemorrhagic	NR	27 (13)	14.9 ± 0.3 months	58.5 ± 1.1
King et al., 2019	Canada	Cohort study	Ischaemic or Haemorrhagic	4.3 ± 4.4	35 (12)	31.5 ± 26.7 months	65.2 ± 9.4
Koroleva et al., 2020	Russia	Cohort study	Ischaemic	NR	50 (28)	0-90 days	64.0 ± 1.7 m (IQR): A-Rehab: 62 (57;67) B-Rehab: 65.5 (60;68)

Study	Country of study	Study type	Stroke type	Stroke severity (NIHSS) (mean ± SD)	Number of participants (number of females)	Time post-stroke (mean ± SD)	Age (years) (mean ± SD)
Mackay et al., 2021	Australia	Pseudo-randomised trial	Ischaemic or Haemorrhagic	NR	20 (5)	3 years and 11 months	60 ± 14
Ploughman et al., 2019	Canada	Block-randomised, single-blinded pilot trial	Ischaemic or Haemorrhagic	Aerobic + COG*: 5.5 ± 3.5 Aerobic + Games†: 4.2 ± 4.2 Activity + COG*: 5.5 ± 5.3 Activity + Games†: 4.4 ± 3.3	52 (16)	41 ± 39.8 months	63.4 ± 11.3
Rahayu et al., 2020	Indonesia	Parallel two-arm RCT	Ischaemic	NR	64 (28)	24 hours	59.4 ± 0.8

Study	Country of study	Study type	Stroke type	Stroke severity (NIHSS) (mean ± SD)	Number of participants (number of females)	Time post-stroke (mean ± SD)	Age (years) (mean ± SD)
Ryan et al., 2019	USA	Longitudinal study	Ischaemic or Haemorrhagic	NR	21 (4)	7 years	43-81
Valkenborghs et al., 2019	Australia	Pilot RCT	Ischaemic or Haemorrhagic	NR	20 (9)	71.7 ± 91.2 months	55.4 ± 16

Abbreviations – SD: Standard deviation; USA: United States of America; NR: Not reported; NIHSS: National Institutes of Health Stroke Scale; RCT: Randomised controlled trial; COG: Cognitive training

* Groups that received computer-based cognitive training.

† Groups that completed non-adaptive computer-based games.

Table 5-3 Interventions and outcome measures

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
Single session of exercise								
Boyne et al., 2020	Symptom-limited GXT	Single session	Maximal effort	High	As long as tolerated	Treadmill	Rest & post-exercise	↑ 4.62 ± 6.14
	MCT-Tread	Single session	45±5% HRR	Moderate	25min	Treadmill	Rest & post-exercise	↓ 0.49 ± 3.98
	HIT-Tread	Single session	>60% HRR	High	25min	Treadmill	Rest & post-exercise	↑ 3.44 ± 5.95
	HIT-Stepper	Single session	>60% HRR	High	25min	Stepper	Rest & post-exercise	↑ 1.59 ± 7.71

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
Charalambous et al., 2018	Control	Single session	25% comfortable walking speed	Low	20min	Treadmill & Split-belt	Rest & post-exercise	↓ 2.35 ± 13.93
	Treadmill Walking	Single session	70-85% age-predicted HR_{max} 13-15/20 RPE	High	20min	Treadmill & Split-belt	Rest & post-exercise	↓ 1.66 ± 7.14
	Total Body Ergometer	Single session	70-85% age-predicted HR_{max} 13-15/20 RPE	High	20min	Total Body Ergometer	Rest & post-exercise	↓ 1.63 ± 10.05

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
De Morais et al., 2018	Session 1	Single session	50-63% HR_{max}	Low	45min	Overground walking	Rest & post-exercise	↓ 0.038
	Session 2	Single session	64-74% HR_{max}	Moderate	45min	Overground walking	Rest & post-exercise	↑ 0.045
King et al., 2019	GXT	Single session	Maximal effort	High	12min 46s ± 6min 4s	Treadmill	Rest & post-exercise	↑ 3
Mackay et al., 2021	Moderate-high intensity	Single session	65% HRR	High	30min	Treadmill	Rest & post-exercise	↑ 3
Program of exercise								
Chang et al., 2018	Standard rehabilitation	2 weeks, PT: 7/week OT: 5/week	NR	Unable to classify	PT: 2 hours OT: 1 hour	PT & OT	Rest, after 1-week of program &	1-week: ↓ 1.24

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
							after 2-weeks of program	2-weeks: ↓ 1.6
Chaturvedi et al., 2020	PNF	2 weeks 5/week	NR	Unable to classify	45min	PNF	Rest & post program	↑ 3.72
Du et al., 2021	LOW	1 week 2/week	40% 1RM	Unable to classify	3 sets of 10 repetitions	Resistance training	Rest & post program	NR
	LOW-BFR	1 week 2/week	40% 1RM	Unable to classify	3 sets of 10 repetitions	Resistance training with BFR cuff on proximal end of moving limb	Rest & post program	NR

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
	HIGH	1 week 2/week	80% 1RM	Unable to classify	3 sets of 10 repetitions	Resistance training	Rest & post program	NR
El-Tamawy et al., 2014	Control	8 weeks 3/week	NR	Unable to classify	25-30min	PT	Rest & post program	↑ 0.18
	Study group	8 weeks 3/week	NR	Unable to classify	75-90min	PT & Cycling	Rest & post program	↑ 4.65
Harnish et al., 2018	Aerobic + CPNT	8 weeks 3/week	Weeks 1+2: 50% HRR Weeks 3-8: 70% HRR	Weeks 1+2: Moderate Weeks 3-8: High	30min	Cycling & CPNT	Rest, mid-program & post program	Pre to mid-program: ↓ 5.50 Mid to post

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
								program: ↑ 2.59 Overall change: ↓ 2.91
	Stretching + CPNT	8 weeks 3/week	“Low”	Unable to classify	50min	Stretching & CPNT	Rest, mid-program & post program	Pre to mid-program: ↑ 2.51 Mid to post program: ↓ 3.61 Overall change: ↓ 0.10

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
Hsu et al., 2021	MICT	12-18 weeks 2-3/week	60% VO_{2peak}	Moderate	36min	Cycling	Rest & post program	↓ 1.42
	HIIT	12-18 weeks 2-3/week	ON: 80% VO_{2peak} OFF: 40% VO_{2peak}	High	36min	Cycling	Rest & post program	↑ 1.85
Kim et al., 2019	Low + Dual-task	6 weeks 5/week	40% VO_{2max}	Low	46.36 ± 3.24min (200kcal)	Treadmill & Cognitive tasks	Rest & post program	↑ 0.77
	Moderate + Dual-task	6 weeks 5/week	55% VO_{2max}	Moderate	35.19 ± 2.83min (200kcal)	Treadmill & Cognitive tasks	Rest & post program	↑ 1.93
	High + Dual-task	6 weeks 5/week	70% VO_{2max}	High	26.24 ± 3.13min (200kcal)	Treadmill & Cognitive tasks	Rest & post program	↑ 4.60

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
Koroleva et al., 2020	A-Rehab	38 days 7/week	NR	Unable to classify	195-207min	Air cryotherapy, FES, Manual classic massage, Mechanotherapy, Therapeutic physical culture & Motor rehabilitation using motion sensor and augmented reality	Rest & post program	↑ 0.01
	B-Rehab	10 days 7/week	NR	Unable to classify	100min	Motor rehabilitation using motion sensor and	Rest & post program	↑ 1.01

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
						augmented reality		
Ploughman et al., 2019	Aerobic + COG	10 weeks 3/week	Aerobic: 60-80% VO_{2peak} COG: Varied difficulty	High	40-60min	Treadmill & Computerised dual-n-back training	Rest, post program & 3-month follow up	Rest to post program: ↓ 3.4 Rest to 3-month follow up: ↓ 6.6
	Aerobic + Games	10 weeks 3/week	Aerobic: 60-80% VO_{2peak} Games: NR	High	40-60min	Treadmill & Non-adaptive computer-based game	Rest, post program & 3-month follow up	Rest to post program: ↓ 2.8 Rest to 3-month

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
								follow up: ↓ 2
	Activity + COG	10 weeks 3/week	Activity: NR COG: Varied difficulty	Unable to classify	40-60min	Massage and active/passive ROM exercises on affected side, Functional task training & Computerised dual-n-back training	Rest, post program & 3-month follow up	Rest to post program: ↑ 1.7 Rest to 3-month follow up: ↓ 6.1
	Activity + Games	10 weeks 3/week	Activity: NR Games: NR	Unable to classify	40-60min	Massage and active/passive ROM exercises on affected side, Functional task	Rest, post program & 3-month follow up	Rest to post program: ↑ 3.1

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
						training & Non-adaptive computer-based game		Rest to 3-month follow up: ↑ 3.11
Rahayu et al., 2020	Neurorestoration intervention	1 week 7/week	Varied according to the participant	Unable to classify	NR	Bobath; PNF; Rood, Carr and Shepherd & CIMT	Rest & post program	↑ 2.62
	Conventional therapy	1 week 7/week	NR	Unable to classify	NR	Position change, breathing exercises and exercises in passive and active mobilisation	Rest & post program	↓ 0.68

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
Ryan et al., 2019	AEX	26 weeks 3/week	60-70% HRR	High	30-50min	Treadmill	Rest & post program	NR
	RT	12 weeks 3/week	10-15 RM	Unable to classify	2 sets of 20 unilateral repetitions	Resistance training	Rest & post program	↑ 0.23*
Valkenborghs et al., 2019	AEX + TST	10 weeks 3/week supervised & 3/week unsupervised	Aerobic – ON: 85% HR_{max} OFF: 70% HR_{max} TST: NR	High	90min supervised 60min unsupervised	Cycling & Whole or part-practice upper limb tasks	Rest & post program	↓ 3.7 ± 12.1
	TST	10 weeks 3/week supervised &	NR	Unable to classify	90min supervised 60min unsupervised	Whole or part-practice upper limb tasks	Rest & post program	↓ 4.7 ± 14.5

Study	Groups	Frequency of intervention	Reported intensity	ACSM aerobic intensity classification	Exercise time	Exercise modality	Time of measure	Change in BDNF (ng/mL)
		3/week unsupervised						

Abbreviations – ACSM: American College of Sports Medicine; BDNF: Brain-Derived Neurotrophic Factor; GXT: Graded exercise test; MCT or MICT: Moderate-intensity continuous training; HRR: Heart rate reserve; HIT or HIIT: High-intensity interval training; PT: Physiotherapy; OT: Occupational therapy; NR: Not reported; HR_{max}: Heart rate maximum; RPE: Rating of perceived exertion; PNF: Proprioceptive Neuromuscular Facilitation; RM: Repetition maximum; BFR: Blood flow restriction; CPNT: Cued picture-naming treatment; MICT: Moderate-intensity continuous training; VO_2peak or VO_2max: Maximal oxygen uptake; kcal: kilocalories; FES: Functional electrical stimulation; COG: Cognitive training; ROM: Range of motion; CIMT: Constraint-induced movement therapy; AEX: Aerobic exercise; RT: Resistance training; TST: Task-specific training.

* Plasma-derived BDNF concentration.

5.5.2 BDNF concentration reporting

Blood-derived BDNF concentration was the primary outcome of interest in this review. All 17 included studies measured BDNF concentration within a peripheral blood sample collected from the stroke participant's vein. All studies collected blood samples at rest prior to the first session of exercise as a baseline BDNF concentration. Sixteen (94%) analysed serum-derived BDNF concentration, with one (6%) study analysing plasma-derived BDNF concentration (Ryan et al., 2019). One (6%) of the included studies collected a mid-program blood sample (Harnish et al., 2018). Two (11%) studies collected a follow up blood sample after the completion of the exercise program, at two-weeks (Chang et al., 2018) and three-months (Ploughman et al., 2019) post-program completion. One (6%) study collected blood samples at four timepoints throughout the study (i.e., day of stroke, at discharge from conventional rehabilitation, post conventional rehabilitation, pre intervention and post intervention) (Koroleva et al., 2020).

Three different methods of BDNF concentration analysis were used within the 17 included studies. Fourteen (82%) of the included studies used the Enzyme-Linked Immunosorbent Assay (ELISA) method (Boyne et al., 2020; Chang et al., 2018; Charalambous et al., 2018; Chaturvedi et al., 2020; de Morais et al., 2018; Du et al., 2021; El-Tamawy et al., 2014; Harnish et al., 2018; Hsu et al., 2021; King et al., 2019; Mackay et al., 2021; Ploughman et al., 2019; Rahayu et al., 2020; Valkenborghs et al., 2019), one (6%) study used the MAGPIX Multiplex Analyser (Koroleva et al., 2020) and one (6%) study used the Human BDNF Emax ImmunoAssay (Ryan et al., 2019). One (6%) study did not specify the BDNF analysis method used, only noting BDNF analysis was outsourced to an external facility (Kim et al., 2019).

BDNF concentration was reported as ng/mL in ten (59%) studies (Chang et al., 2018; Charalambous et al., 2018; Chaturvedi et al., 2020; El-Tamawy et al., 2014; Hsu et al., 2021; King et al., 2019; Mackay et al., 2021; Ploughman et al., 2019; Ryan et al., 2019; Valkenborghs et al., 2019), ng/L in one (6%) study (Boyne et al., 2020), and pg/mL in six (35%) of the included studies (de Morais et al., 2018; Du et al., 2021; Harnish et al., 2018; Kim et al., 2019; Koroleva et al., 2020; Rahayu et al., 2020). Fourteen (82%) studies reported the BDNF concentration results as mean ± SD (Boyne et al., 2020; Chang et al., 2018; Charalambous et al., 2018; Chaturvedi et al., 2020; de Morais et al., 2018; El-Tamawy et al.,

2014; Harnish et al., 2018; Hsu et al., 2021; Kim et al., 2019; King et al., 2019; Mackay et al., 2021; Ploughman et al., 2019; Ryan et al., 2019; Valkenborghs et al., 2019). One (6%) reported the results as median and interquartile range (Koroleva et al., 2020), and one (6%) reported the results as mean and 95% confidence interval (Rahayu et al., 2020). One (6%) study did not report the numerical results for BDNF concentration (Du et al., 2021).

Blood-derived BDNF concentrations were reported pre- and post-intervention for twenty-six (70%) of the included 37 interventions. Of the remaining eleven interventions, the change in BDNF concentration between pre- and post-intervention were reported for seven interventions (Boyne et al., 2020; Charalambous et al., 2018), only the significance of the change was reported for three interventions (Du et al., 2021) and no results were reported for one intervention (Ryan et al., 2019). Study authors were emailed to obtain BDNF concentration data following the exercise interventions provided. One author reported that changes in BDNF concentration were not calculated for the aerobic exercise group (Ryan et al., 2019), and one author could not be contacted (Du et al., 2021). Individual participant BDNF concentrations for each timepoint were provided for seven (19%) interventions (Boyne et al., 2020; Charalambous et al., 2018), these were then averaged to calculate a group mean.

5.5.3 Intervention characteristics

Of the 17 included studies in this systematic review, 16 examined the effects of at least two separate exercise interventions on BDNF concentration, with the number of interventions per study ranging from one to four. The intensity of the exercise interventions within the included studies were reported using various physiological measures. Five (29%) studies (Chang et al., 2018; Chaturvedi et al., 2020; El-Tamawy et al., 2014; Koroleva et al., 2020; Rahayu et al., 2020) did not report the intensity of the exercise intervention provided. Two studies (12%) studies (Ploughman et al., 2019; Valkenborghs et al., 2019) did not report the intensity of one of the included interventions, and authors of one study provided details of the exercise intensity classification used within the intervention via personal correspondence (Harnish et al., 2018). Therefore, 11 of the 37 exercise interventions could not be classified according to exercise intensity due to this information not being provided.

5.5.3.1 Frequency

Five (29%) of the included studies examined the effect of a single bout of exercise on blood-derived BDNF concentration (Boyne et al., 2020; Charalambous et al., 2018; de Morais et al., 2018; King et al., 2019; Mackay et al., 2021), and the remaining twelve studies (71%) examined the effect of a program of exercise. The duration of the program interventions ranged from one to 26 weeks, with participants completing a mean ± SD of 24 ± 16 sessions (range, 2-78 sessions). The frequency of sessions completed within the programs of exercise in the included studies ranged from twice per week to daily.

5.5.3.2 Intensity

Within the studies reporting exercise intensity, seven different measures of intensity were utilised. Exercise intensity was reported as percentage of heart rate maximum (%HRmax) in three studies (Charalambous et al., 2018; de Morais et al., 2018; Valkenborghs et al., 2019) and heart rate reserve (%HRR) in four studies (Boyne et al., 2020; Harnish et al., 2018; Mackay et al., 2021; Ryan et al., 2019). Volume of maximal oxygen uptake (i.e., %VO2max) was used in three studies (Boyne et al., 2020; Kim et al., 2019; King et al., 2019) and volume of peak oxygen uptake (i.e., %VO2peak) in two studies (Hsu et al., 2021; Ploughman et al., 2019). Percentage of comfortable walking speed was also utilised in one study (Charalambous et al., 2018) to report exercise intensity. Two studies prescribed resistance exercise using repetition maximum as a percentage (i.e., %RM) or the absolute value (RM) of the total number of repetitions the participant could successfully complete (Du et al., 2021; Ryan et al., 2019).

In accordance with the ACSM aerobic exercise intensity cut-offs (e.g., heart rate, maximal oxygen consumption, etc.) (Table 5-1) (Pescatello, 2014), four interventions were classified as ‘low’ intensity (Charalambous et al., 2018; de Morais et al., 2018; Harnish et al., 2018; Kim et al., 2019), four interventions were classified as ‘moderate’ intensity (Boyne et al., 2020; de Morais et al., 2018; Hsu et al., 2021; Kim et al., 2019) and fifteen interventions were classified as ‘high’ intensity (Boyne et al., 2020; Charalambous et al., 2018; Harnish et al., 2018; Hsu et al., 2021; Kim et al., 2019; King et al., 2019; Mackay et al., 2021; Ploughman et al., 2019; Ryan et al., 2019; Valkenborghs et al., 2019). One study provided an aerobic exercise and cognitive training intervention which began at ‘moderate’ intensity for the first

two weeks and increased to 'high' intensity for the final five weeks (Harnish et al., 2018). The intensity of one aerobic intervention was not provided (El-Tamawy et al., 2014). Fifteen interventions utilised non-aerobic modalities, therefore intensity was unable to be classified using the ACSM aerobic exercise intensity classifications (Chang et al., 2018; Chaturvedi et al., 2020; Du et al., 2021; El-Tamawy et al., 2014; Koroleva et al., 2020; Ploughman et al., 2019; Rahayu et al., 2020; Ryan et al., 2019; Valkenborghs et al., 2019).

5.5.3.3 Time

The duration of each exercise session was reported in 16 (94%) of the 17 included studies, with Rahayu et al. (2020) not reporting the duration of the prescribed intervention. Mean ± SD duration of all 37 interventions included in this review was 59 ± 48 min. Mean duration of the single-session exercise intervention (27 ± 11 min) was shorter compared to multi-session programs (74 ± 52 min).

5.5.3.4 Modality

Aerobic exercise was utilised in 22 of the 37 interventions (Boyne et al., 2020; Charalambous et al., 2018; de Morais et al., 2018; El-Tamawy et al., 2014; Harnish et al., 2018; Hsu et al., 2021; Kim et al., 2019; King et al., 2019; Mackay et al., 2021; Ploughman et al., 2019; Ryan et al., 2019; Valkenborghs et al., 2019). Two interventions employed a maximal aerobic exercise protocol (Boyne et al., 2020; King et al., 2019), four used interval training (Boyne et al., 2020; Hsu et al., 2021; Valkenborghs et al., 2019) and the remaining 31 interventions were continuous programs of a set intensity.

Non-aerobic interventions such as augmented reality training (Koroleva et al., 2020), conventional therapies (e.g., physiotherapy, occupational therapy) (Chang et al., 2018; El-Tamawy et al., 2014; Rahayu et al., 2020), dual therapies of non-aerobic nature (e.g., physical activities and cognitive interventions) (Koroleva et al., 2020; Ploughman et al., 2019). flexibility training (Chaturvedi et al., 2020; Harnish et al., 2018), resistance training (Du et al., 2021; Ryan et al., 2019) and upper-limb therapy (Valkenborghs et al., 2019) were utilised in 15 interventions.

5.5.4 Methodological quality assessment

Of the six randomised trials assessed using the RoB 2 tool, two (33%) were categorised as 'Low' risk of bias (Ploughman et al., 2019; Valkenborghs et al., 2019) and four (67%) were categorised as having 'Some Concerns' (Du et al., 2021; Hsu et al., 2021; Kim et al., 2019; Rahayu et al., 2020) (Table 5-4).

Of the 11 non-randomised trials assessed using the ROBINS-I tool, nine (82%) were classified as a 'Low' risk of bias (Boyne et al., 2020; Charalambous et al., 2018; Chaturvedi et al., 2020; de Morais et al., 2018; El-Tamawy et al., 2014; Harnish et al., 2018; King et al., 2019; Koroleva et al., 2020; Mackay et al., 2021), and two (18%) were classified as 'Moderate' risk of bias (Chang et al., 2018; Ryan et al., 2019) (Table 5-5).

The certainty of evidence was varied across the different intensities, modalities and durations of exercise interventions provided, all assessed using the GRADE approach (Brozek et al., 2009). High certainty of evidence was determined for the studies examining a single session of low, moderate, and high intensity aerobic exercise, as well as a program of high intensity aerobic exercise (Table 5-6). Low certainty of evidence was determined for a program of moderate intensity aerobic exercise (Table 5-6). Moderate certainty of evidence was determined for a program of non-aerobic exercise (Table 5-6).

Table 5-4 Methodological quality assessment of the included randomised trials using the RoB 2 tool (Sterne et al., 2019)

Study	Risk of bias arising from the randomisation process	Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall risk of bias
Du et al., 2021	Some concerns	Some concerns	Low	Low	Low	Some concerns
Hsu et al., 2021	Some concerns	Low	Low	Low	Low	Some concerns
Kim et al., 2019	Some concerns	Low	Low	Low	Low	Some concerns
Ploughman et al., 2019	Low	Low	Low	Low	Low	Low
Rahayu et al., 2020	Some concerns	Low	Low	Low	Low	Some concerns
Valkenborghs et al., 2019	Low	Low	Low	Low	Low	Low

Table 5-5 Methodological quality assessment of the included non-randomised trials using the ROBINS-I tool (Sterne et al., 2016)

Study	Risk of bias due to confounding	Risk of bias in selection of participants into the study	Risk of bias in classification of intervention	Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias due to missing data	Risk of bias in measurement of outcomes	Risk of bias in selection of the reported results	Overall risk of bias
Boyne et al., 2020	Low	Low	Low	Low	Low	Low	Low	Low
Chang et al., 2018	Low	Low	Serious	Low	Low	Low	Low	Moderate
Charalambous et al., 2018	Low	Low	Low	Low	Low	Low	Low	Low
Chaturvedi et al., 2020	Low	Low	Low	Low	Low	Low	Low	Low

Study	Risk of bias due to confounding	Risk of bias in selection of participants into the study	Risk of bias in classification of intervention	Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias due to missing data	Risk of bias in measurement of outcomes	Risk of bias in selection of the reported results	Overall risk of bias
de Morais et al., 2018	Low	Low	Low	Low	Low	Low	Low	Low
El-Tamawy et al., 2014	Low	Low	Low	Low	Low	Low	Low	Low
Harnish et al., 2018	Low	Low	Low	Low	Low	Low	Low	Low
King et al., 2019	Low	Low	Low	Low	Low	Low	Low	Low
Koroleva et al., 2020	Low	Low	Low	Low	Low	Low	Low	Low

Study	Risk of bias due to confounding	Risk of bias in selection of participants into the study	Risk of bias in classification of intervention	Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias due to missing data	Risk of bias in measurement of outcomes	Risk of bias in selection of the reported results	Overall risk of bias
Mackay et al., 2021	Low	Low	Low	Low	Low	Low	Low	Low
Ryan et al., 2019	Low	Low	Low	Low	Moderate	Low	Low	Moderate

Table 5-6 GRADE Approach for certainty of evidence (Brozek et al., 2009)

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Post-exercise**	**Pre-exercise**	**Relative (95% CI)**	**Absolute (95% CI)**	
2	observational studies	not serious	not serious	not serious	serious[a]	strong association all plausible residual confounding would reduce demonstrated effect dose response gradient	23	23	-	MD **0.04 lower** (0.3 lower to 0.22 higher)	⨁⨁⨁⨁ High
2	observational studies	not serious	not serious	not serious	serious[a]	all plausible residual confounding would reduce demonstrated	26	26	-	MD **0.04 higher** (0.21 lower	⨁⨁⨁⨁ High

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Post-exercise**	**Pre-exercise**	**Relative (95% CI)**	**Absolute (95% CI)**	
						effect dose response gradient				to 0.3 higher)	
4	observational studies	not serious	serious[b]	not serious	not serious	very strong association all plausible residual confounding would reduce demonstrated effect dose response gradient	127	127	-	MD **2.49** **higher** (1.1 higher to 3.88 higher)	⨁⨁⨁⨁ High
3	observational studies	serious[c]	serious[d]	not serious	very serious[a]	all plausible residual	26	26	-	MD **0.22**	⨁⨁◯◯ Low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Post-exercise**	**Pre-exercise**	**Relative (95% CI)**	**Absolute (95% CI)**	
						confounding would reduce demonstrated effect dose response gradient				**lower** (3.31 lower to 2.88 higher)	
5	observational studies	serious[e]	serious[f]	not serious	not serious	very strong association all plausible residual confounding would reduce demonstrated effect dose	60	60	-	MD **3.42 higher** (1.92 higher to 4.92 higher)	⨁⨁⨁⨁ High

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Post-exercise**	**Pre-exercise**	**Relative (95% CI)**	**Absolute (95% CI)**	
						response gradient					
9	observational studies	serious[g]	serious[h]	serious[i]	not serious	all plausible residual confounding would reduce demonstrated effect dose response gradient	415	415	-	MD **0.72 higher** (0.05 lower to 1.5 higher)	⨁⨁◯◯ Low

Abbreviations – CI: confidence interval; MD: mean difference

Explanations:

a. 95% CI crosses the threshold of zero.

b. Wide spread of results with MD (95% CI) ranging from -1.65 (-6.23, 2.93) to 4.76 (-1.65, 11.17).

c. ROB 2 analysis of the two randomised trials (Kim et al., 2019; Hsu et al., 2021) demonstrated some concerns due to risk of bias arising from the randomisation process and deviations from the intended interventions (effect of assignment to intervention). ROBINS-I analysis of risk of bias was low for the included before-after study (Harnish et al., 2018).

d. Wide spread of results with MD (95% CI) ranging from -5.50 (-16.25, 5.26) to 1.93 (-0.02, 2.88).

e. ROB 2 analysis of two randomised trials (Kim et al., 2019; Hsu et al., 2021) demonstrated some concerns due to risk of bias arising from the randomisation process and deviations from the intended interventions (effect of assignment to intervention). ROB 2 analysis of two randomised trials (Ploughman et al., 2019; Valkenborghs et al., 2019) were low risk of bias. ROBINS-I analysis of risk of bias was low for the included before-after study (Harnish et al., 2018).

f. Wide spread of results with MD (95% CI) ranging from -3.70 (-15.26, 7.86) to 4.60 (2.68, 6.52).

g. ROB 2 analysis of one of two randomised trials (Rahayu et al., 2020) demonstrate some concerns due to risk of bias arising from the randomisation process and deviations from the intended interventions (effect of assignment to intervention). The ROB 2 analysis of the other included randomised trials (Ploughman et al., 2019; Valkenborghs et al., 2019) demonstrate low risk of bias. ROBINS-I analysis of two of the included before-after studies demonstrate moderate risk of bias due to serious concerns for the risk of classification of intervention (Chang et al. 2018) and moderate concerns for risk of bias due to missing data (Ryan et al., 2019). The ROBINS-I analysis of the other included before-after studies (Chaturvedi et al., 2020; El-Tamawy et al., 2014; Harnish et al., 2018; Koroleva et al., 2020) demonstrate low risk of bias.

h. Wide spread of results with MD (95% CI) ranging from -4.70 (-13.75, 4.35) to 3.72 (2.98, 4.46). The results of one study (Harnish et al., 2018) were not estimable due to a sample size of one participant.

i. BDNF analysis was completed using the Enzyme-Linked Immunosorbent Assay (ELISA) method in seven studies (Chang et al., 2018; Chaturvedi et al., 2020; El-Tamawy et al., 2014; Harnish et al., 2018; Ploughman et al., 2019; Rahayu et al., 2020; Valkenborghs et al., 2019.) The MAGPIX Multiplex Analyser method was used in one study (Koroleva et al., 2020). The Human BDNF Emax ImmunoAssay was used in one study (Ryan et al., 2019).

5.5.5 Effect of a single session of exercise

Five (29%) studies evaluated the effect of a single session of aerobic exercise on blood-derived BDNF concentration (Boyne et al., 2020; Charalambous et al., 2018; de Morais et al., 2018; King et al., 2019; Mackay et al., 2021).

5.5.5.1 Effect of a single session of low intensity aerobic exercise

Two interventions were classified as low intensity aerobic exercise (Charalambous et al., 2018; de Morais et al., 2018). Both demonstrated a decrease in BDNF concentration post-session, ranging from -2.36 to -0.0375 ng/mL. Based on statistical and clinical homogeneity of the studies, both interventions were included in a fixed effects meta-analysis (Figure 5-2A). Results show a small, non-significant effect of a single session of low intensity aerobic exercise on BDNF concentration, which favours the control over the intervention from pre- to post-exercise BDNF concentration (MD -0.04, 95% CI -0.30 to 0.22, p = 0.76), with a low observed heterogeneity between studies (I^2 = 0%, p = 0.59) and high certainty (Table 5-6).

5.5.5.2 Effect of a single session of moderate intensity aerobic exercise

Two interventions were classified as moderate intensity aerobic exercise (Boyne et al., 2020; de Morais et al., 2018), demonstrating mixed effects on BDNF concentration post-session. The observed changes in BDNF concentration following a single session of moderate intensity aerobic exercise ranged from -0.492 to 0.0448 ng/mL. Based on statistical and clinical homogeneity of studies, both interventions were included in a fixed effects meta-analysis (Figure 5-2B). Results show a small, non-significant effect of a single session of moderate intensity aerobic exercise on BDNF concentration, which favours the intervention over the control from pre- to post-exercise BDNF concentration (MD 0.04, 95% CI -0.21 to 0.30, p = 0.73), with a low observed heterogeneity between studies (I^2 = 0%, p = 0.86) and high certainty (Table 5-6).

5.5.5.3 Effect of a single session of high intensity aerobic exercise

Seven interventions were classified as high intensity aerobic exercise (Boyne et al., 2020; Charalambous et al., 2018; King et al., 2019; Mackay et al., 2021). Five (71%) of the included seven interventions produced an increase in BDNF concentration post-session (Boyne et al.,

2020; King et al., 2019; Mackay et al., 2021). Observed changes in BDNF concentration following a single session of high intensity aerobic exercise ranged from -1.65 to 4.761 ng/mL, with larger increases observed following maximal efforts (Boyne et al., 2020; King et al., 2019) and high intensity interval training (Boyne et al., 2020). Based on statistical and clinical homogeneity of studies, all seven interventions were included in a fixed effects meta-analysis (Figure 5-2C). Results show a very large, statistically significant effect of a single session of high intensity aerobic exercise on blood-derived BDNF concentration, which favours the intervention over the control from pre- to post-exercise BDNF concentration (MD 2.49, 95% CI 1.10 to 3.88, p = 0.0005), with a low observed heterogeneity between studies (I^2 = 0%, p = 0.55) and high certainty (Table 5-6).

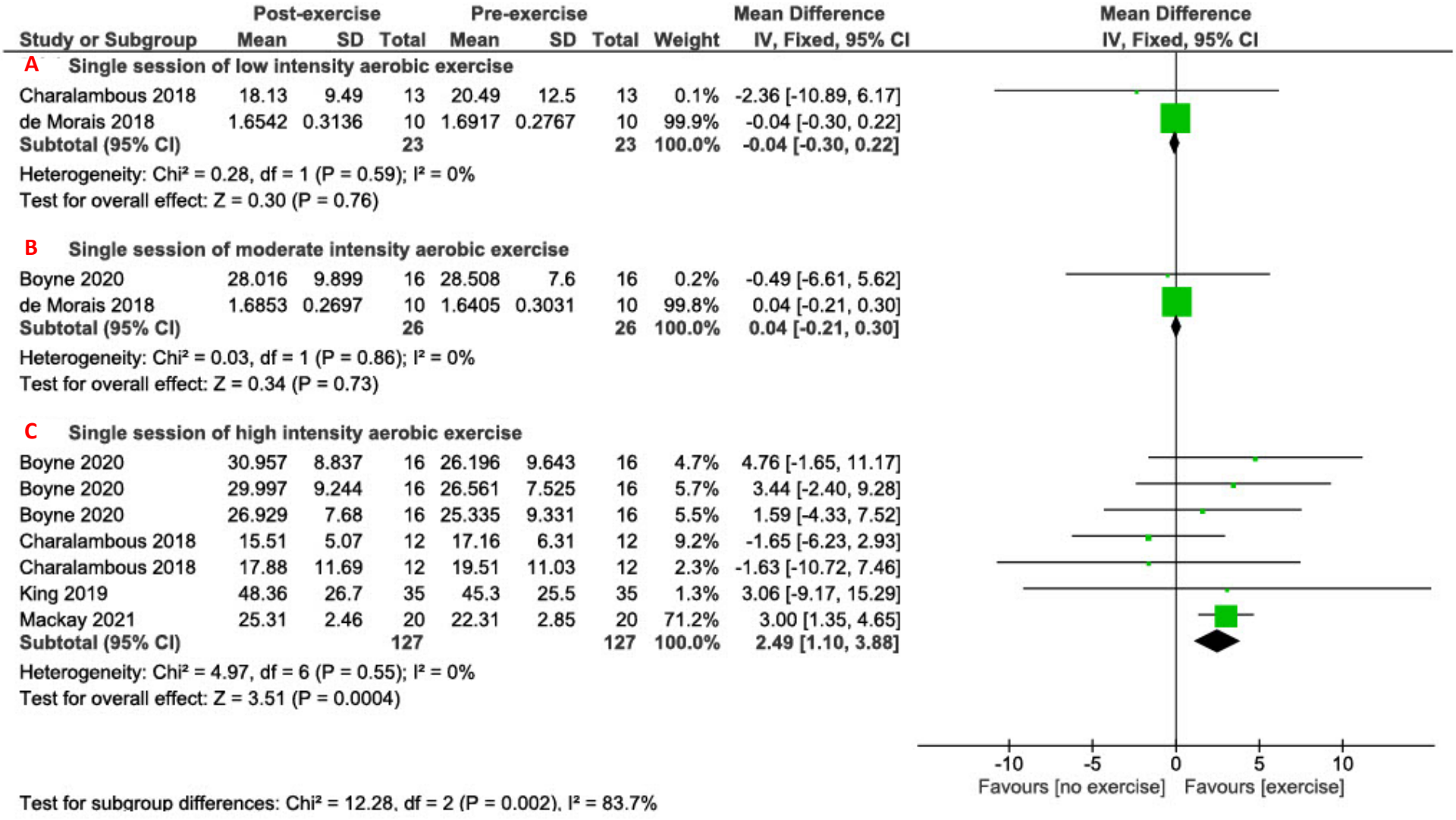


Figure 5-2 Meta-analysis of the effects of a single session of aerobic exercise (fixed effects)

5.5.6 Effect of a program of exercise

Twelve (71%) of the included studies evaluated the change in blood-derived BDNF concentration following a program of exercise (Chang et al., 2018; Chaturvedi et al., 2020; Du et al., 2021; El-Tamawy et al., 2014; Harnish et al., 2018; Hsu et al., 2021; Kim et al., 2019; Koroleva et al., 2020; Ploughman et al., 2019; Rahayu et al., 2020; Ryan et al., 2019; Valkenborghs et al., 2019). Within these studies, twenty-six interventions were utilised, eleven (42%) aerobic (El-Tamawy et al., 2014; Harnish et al., 2018; Hsu et al., 2021; Kim et al., 2019; Ploughman et al., 2019; Ryan et al., 2019; Valkenborghs et al., 2019) and 15 (58%) non-aerobic (i.e., unable to be classified according to the ACSM aerobic exercise intensity classifications) (Chang et al., 2018; Chaturvedi et al., 2020; Du et al., 2021; El-Tamawy et al., 2014; Harnish et al., 2018; Koroleva et al., 2020; Ploughman et al., 2019; Rahayu et al., 2020; Ryan et al., 2019; Valkenborghs et al., 2019).

5.5.6.1 Effect of a program of aerobic exercise

Of the 11 aerobic intervention programs included in this review (El-Tamawy et al., 2014; Harnish et al., 2018; Hsu et al., 2021; Kim et al., 2019; Ploughman et al., 2019; Ryan et al., 2019; Valkenborghs et al., 2019), 10 (91%) interventions provided the exercise intensity completed. Two interventions were omitted from meta-analysis because the intensity of exercise was not reported (El-Tamawy et al., 2014) and one did not report BDNF concentration at any time point (Ryan et al., 2019). One intervention increased the intensity of exercise mid-program, increasing from 'Moderate' to 'High' (Harnish et al., 2018). This program was analysed as two separate interventions as BDNF concentration was calculated at three timepoints (at rest, mid-program before an increase in exercise intensity, and post-program). Therefore, a total of ten interventions were analysed.

5.5.6.1.1 Effect of a program of low intensity aerobic exercise

One program of low intensity aerobic exercise demonstrated an increase in BDNF concentration following the completion of the exercise program (Kim et al., 2019). This result shows a large, statistically non-significant effect of a program of low intensity aerobic exercise, which favours the intervention over the control from pre- to post-exercise BDNF concentration (MD 0.77, 95% CI -0.83 to 2.38, p = 0.35).

5.5.6.1.2 Effect of a program of moderate intensity aerobic exercise

Three interventions provided a program of moderate intensity aerobic exercise (Harnish et al., 2018; Hsu et al., 2021; Kim et al., 2019). One program produced an increase in BDNF concentration (Kim et al., 2019). Observed changes in BDNF concentration following the completion of a moderate intensity aerobic exercise program ranged from -5.499 to 1.927 ng/mL. Based on statistical and clinical homogeneity of the studies, all three interventions were included in a random effects meta-analysis (Figure 5-3). Results show a small, statistically non-significant effect of a program of moderate intensity aerobic exercise on blood-derived BDNF concentration, which favours the control over the intervention from pre- to post-exercise BDNF concentration (MD -0.22, 95% CI -3.31 to 2.88, p = 0.89), with considerable heterogeneity between studies (I^2 = 75%, p = 0.02) and low certainty (Table 5-6).

Study or Subgroup	Post-exercise Mean	SD	Total	Pre-exercise Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Harnish 2018	18.055	7.408	4	23.554	8.096	4	7.2%	-5.50 [-16.25, 5.26]
Hsu 2021	5.88	1.92	13	7.3	2.044	13	48.1%	-1.42 [-2.94, 0.10]
Kim 2019	21.455	2.196	9	19.528	2.021	9	44.7%	1.93 [-0.02, 3.88]
Total (95% CI)			**26**			**26**	**100.0%**	**-0.22 [-3.31, 2.88]**

Heterogeneity: Tau² = 4.57; Chi² = 7.96, df = 2 (P = 0.02); I² = 75%

Test for overall effect: Z = 0.14 (P = 0.89)

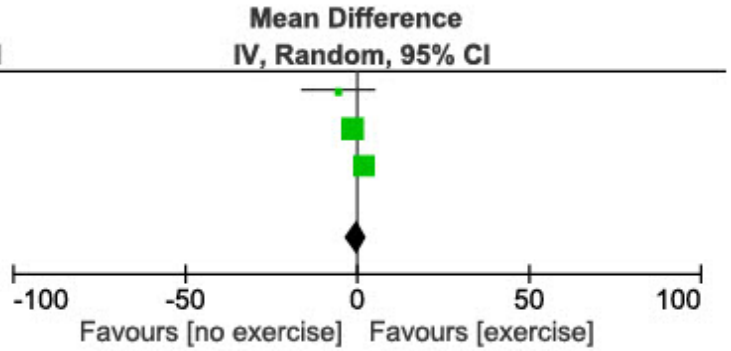


Figure 5-3 Meta-analysis of the effects of a program of moderate intensity aerobic exercise (random effects)

5.5.6.1.3 Effect of a program of high intensity aerobic exercise

Six interventions provided a high intensity exercise program (Harnish et al., 2018; Hsu et al., 2021; Kim et al., 2019; Ploughman et al., 2019; Valkenborghs et al., 2019). Two (33%) programs produced an increase in BDNF concentration (Hsu et al., 2021; Kim et al., 2019). Observed changes in BDNF concentration following the completion of a high intensity aerobic exercise program ranged from -3.7 to 4.604 ng/mL. Based on statistical and clinical homogeneity of studies, all six interventions were included in a fixed effects meta-analysis (Figure 5-4). Results show a very large, statistically significant effect of a program of aerobic exercise on blood-derived BDNF concentration, which favours the intervention over the control from pre- to post-exercise BDNF concentration (MD 3.42, 95% CI 1.92 to 4.92, p = 0.00), with a low heterogeneity between studies (I^2 = 2%, p = 0.41) and high certainty (Table 5-6).

Study or Subgroup	Post-exercise Mean	SD	Total	Pre-exercise Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Harnish 2018	20.647	7.777	7	18.055	7.408	7	3.6%	2.59 [-5.36, 10.55]
Hsu 2021	7.91	2.866	10	6.06	3.159	10	32.3%	1.85 [-0.79, 4.49]
Kim 2019	23.596	2.067	9	18.992	2.088	9	61.3%	4.60 [2.68, 6.52]
Ploughman 2019	32.3	29.55	12	35.7	38.11	12	0.3%	-3.40 [-30.68, 23.88]
Ploughman 2019	26.5	19.11	13	29.3	24.5	13	0.8%	-2.80 [-19.69, 14.09]
Valkenborghs 2019	20.4	12.1	9	24.1	12.9	9	1.7%	-3.70 [-15.26, 7.86]
Total (95% CI)			**60**			**60**	**100.0%**	**3.42 [1.92, 4.92]**

Heterogeneity: Chi² = 5.08, df = 5 (P = 0.41); I² = 2%

Test for overall effect: Z = 4.46 (P < 0.00001)

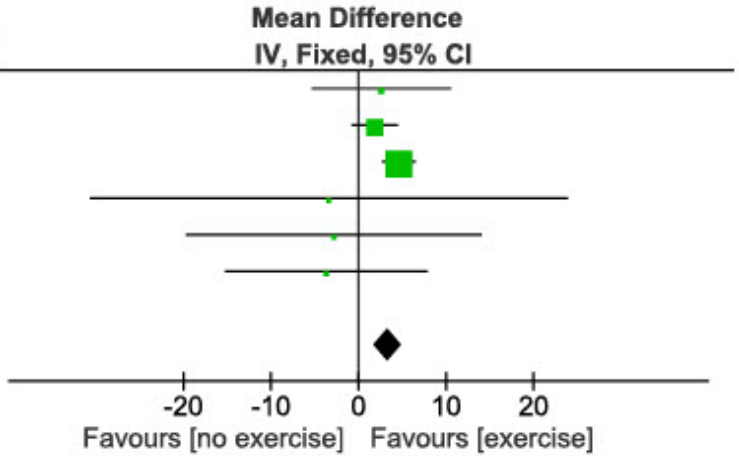


Figure 5-4 Meta-analysis of the effects of a program of high intensity aerobic exercise (fixed effects)

5.5.6.1.4 Effect of a program of non-aerobic exercise

Fifteen interventions did not include targeted aerobic exercise (Chang et al., 2018; Chaturvedi et al., 2020; Du et al., 2021; El-Tamawy et al., 2014; Harnish et al., 2018; Koroleva et al., 2020; Ploughman et al., 2019; Rahayu et al., 2020; Ryan et al., 2019; Valkenborghs et al., 2019). Eight (53%) of the 15 non-aerobic exercise programs demonstrated an increase in BDNF concentration following the intervention (Chaturvedi et al., 2020; El-Tamawy et al., 2014; Koroleva et al., 2020; Ploughman et al., 2019; Rahayu et al., 2020; Ryan et al., 2019). Observed changes in BDNF concentration following the completion of a non-aerobic exercise program ranged from -4.7 ng/mL to 3.72 ng/mL. Based on statistical and clinical homogeneity of studies, 12 interventions (80%) were included in a random effects meta-analysis (Figure 5-5). Results show a medium, non-significant effect, which favours exercise (MD 0.72, 95% CI -0.05 to 1.50, p = 0.07), with considerable heterogeneity and low certainty (Table 5-6).

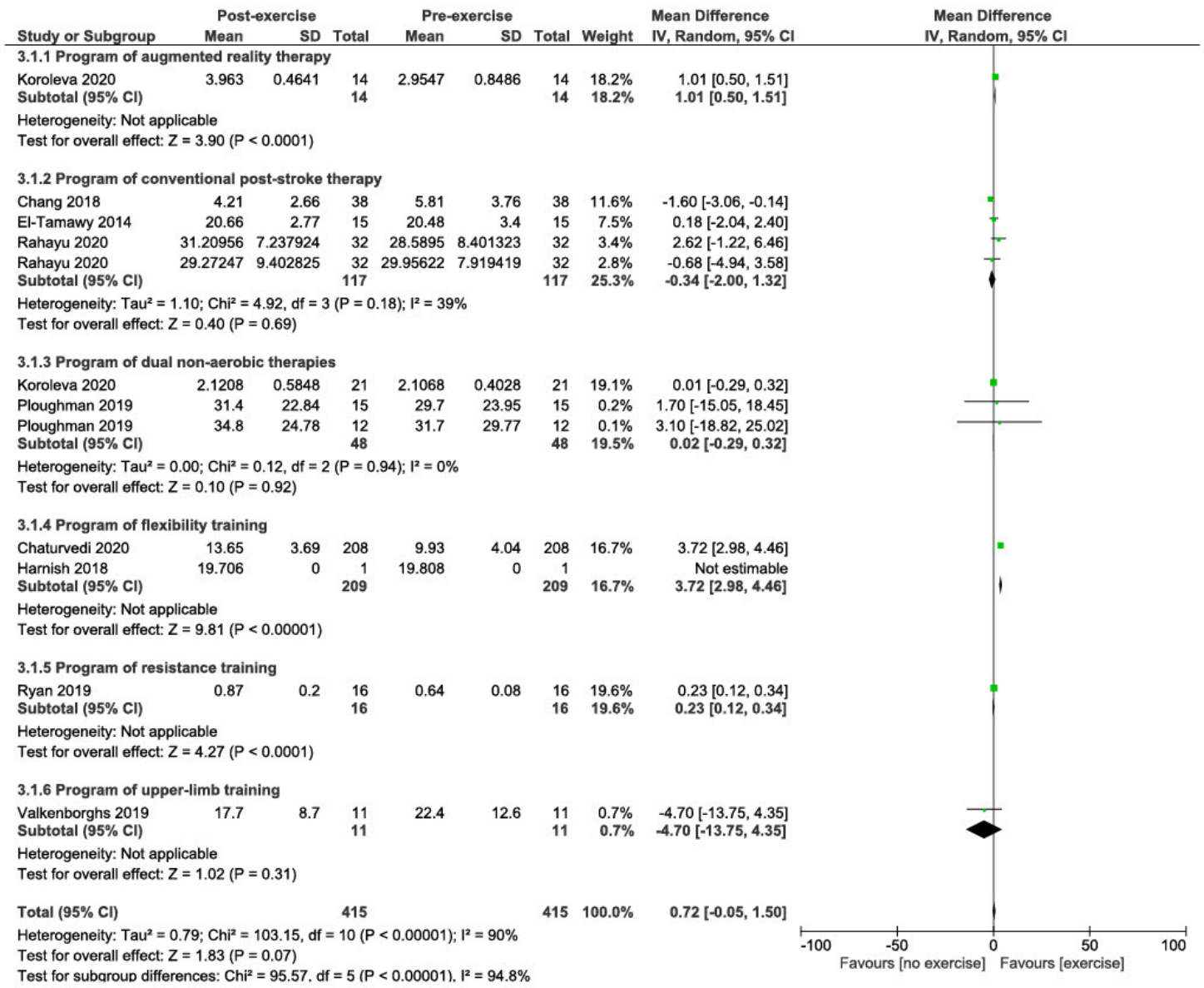


Figure 5-5 Meta-analysis of the effect of a program of non-aerobic exercise (random effects)

5.6 Discussion

This systematic review and meta-analysis demonstrate increased BDNF concentration following high intensity aerobic exercise and, though smaller and non-significant, also following a program of non-aerobic exercise.

The results support the use of aerobic exercise as a preferred mode of exercise to optimally increase BDNF concentrations within post-stroke human adults. A single session or program of high intensity aerobic exercise produced very large, significant effects on BDNF concentration (MD 2.49 ng/mL and 3.42 ng/mL, respectively). A very large, significant effect on BDNF concentration was also observed following a program of non-aerobic modality exercise (MD 0.89 ng/mL).

These results are consistent with existing literature demonstrating aerobic exercise as a means of increasing blood-derived BDNF concentrations in neurological populations (Mackay et al., 2017), including people with stroke (Alcantara et al., 2018; Mojtabavi et al., 2022). Rat stroke studies have demonstrated transient increases in BDNF concentration following a single session of aerobic exercise, with increases diminishing after approximately two hours post-exercise (Rasmussen et al., 2009). However, emerging evidence in healthy human cohorts suggests that the implementation of a program of aerobic exercise may have the potential to produce more sustained increases in BDNF concentration (Griffin et al., 2011). This may be attributed to the higher peak concentrations of BDNF achieved following multiple acute aerobic exercise bouts (Griffin et al., 2011), or the capacity of a program of aerobic exercise to increase the basal concentrations of BDNF within the body (Seifert et al., 2010). Despite these studies being conducted in otherwise healthy subjects, the results of this systematic review support this hypothesis, with larger increases in BDNF concentration demonstrated following a program of high intensity aerobic exercise compared to a single session.

The results of this review also support existing evidence suggesting that non-aerobic training, in particular resistance training and functional-task training, produce minimal effects on BDNF concentration. Resistance training completed by healthy adults in isolation

appears to produce little effect on BDNF concentration (Dinoff et al., 2016; Yarrow et al., 2010), but a large effect is observed when resistance exercises are combined with aerobic exercise in a program of exercise (Canton-Martínez et al., 2022). Similarly, functional exercises such as reaching tasks elicit small increases in BDNF concentration in rat cohorts, with larger increases observed in combined reaching and aerobic exercise (Ploughman et al., 2007). These results suggest the inclusion of aerobic exercise within a multi-disciplinary rehabilitation program is important to drive changes in circulating BDNF concentrations. These results suggest the intensity of the exercise training is critical to the magnitude of change in BDNF concentration.

A larger mean difference in the change from resting to post-exercise BDNF concentrations was observed after a single session or program of high intensity aerobic exercise when compared to low or moderate intensity aerobic exercise. This is a first time finding for this population but are consistent with what has been observed in studies of apparently healthy young adults comparing the effect of exercise intensity on BDNF concentration (Fernández-Rodríguez et al., 2021; Rojas Vega et al., 2006).

While the exact mechanisms underlying this finding are unclear, larger increases in BDNF concentration associated with higher intensity aerobic exercise may be attributed to increased synthesis of BDNF within the brain and subsequent distribution throughout the body (Jiménez-Maldonado et al., 2018). High intensity aerobic exercise results in the robust upregulation of Peroxisome Proliferator-Activated Receptor-Gamma Coactivator 1 Alpha (PGC-1α), a regulator of cell aerobic metabolism (Brandt et al., 2017). The increased levels of PGC-1α, through the PGC1α and Fibronectin Type III Domain-Containing 5 (FNDC5) pathway by which BDNF expression is mediated, therefore results in increased concentrations of BDNF synthesised and released into the bloodstream (El Hayek et al., 2019). A positive correlation between BDNF concentration and lactate, a blood marker frequently used as a measure of exercise intensity (i.e., lactate concentration increases with increasing exercise intensity) has previously been found (Schiffer et al., 2011). Lactate has been proven to mediate the induction of the PGC-1α protein (El Hayek et al., 2019), thereby supporting the increased rates of synthesis and expression of BDNF within the PGC-1α/FNDC5 pathway in response to exercise (Mueller et al., 2020).

Optimising exercise interventions to increase BDNF concentration may assist with improvements in functional outcomes post-stroke. There is a negative correlation between BDNF concentration and stroke severity (Wang et al., 2019), functional disability post-stroke and stroke risk (Stanne et al., 2016). BDNF is also a crucial mediator of motor learning, facilitated through exercise (Ploughman et al., 2009), with a positive relationship between BDNF concentration and motor function recovery rate (Ploughman et al., 2009; Sun et al., 2014). Within the included studies, improvements in upper limb function following high intensity aerobic training were evident in a sensorimotor adaptation test using a digitised pen and tablet (Mackay et al., 2021). In addition, improvements in Action Research Arm Test results were demonstrated following a program of HIIT and TST, however no added benefit of aerobic exercise was demonstrated in the WMFT or MAL results when compared to TST alone (Valkenbourghs et al., 2019). The inclusion of aerobic exercise demonstrated improvements in cognitive function when completed with physiotherapy (El-Tamawy et al., 2014) and dual-task training (Kim et al., 2019). Greater effects of aphasia therapy were demonstrated when the intervention was paired with aerobic exercise as opposed to flexibility training (Harnish et al., 2018). Therefore, it is possible that utilising exercise to increase BDNF concentration may enhance functional improvements following other therapy modalities, however further studies are required.

5.6.1 Limitations

This systematic review and meta-analysis is not without its limitations.

Few randomised trials were identified in the literature search, requiring two separate methodological assessment tools to increase the validity of the assessment. Many studies omitted relevant information regarding the intervention and/or the outcome measures, and despite the research teams best efforts to acquire this information from study authors, less than a third responded to attempts at contact. While 12 (75%) studies examined BDNF changes as the primary outcome, the sample sizes of the included studies were variable and there was little evidence of studies recruiting samples that were powered for a change in BDNF concentration. Considerable heterogeneity was observed in the meta-analysis of a program of moderate intensity aerobic exercise (I^2 = 75%) and a program of non-aerobic exercise (I^2 = 90%). Consequently, a random effects model was used in the meta-analysis of these interventions. This heterogeneity may be associated with the differences in

participant cohorts, such as the variability of stroke severity, which may impact the conclusions we can draw from this study given BDNF concentration has been found to be negatively correlated with NIHSS scores (Qiao et al., 2017). However, this is representative of real-world stroke rehabilitation and may assist in the generalisability of these results to clinical practice where stroke survivors' cohorts are not homogenous.

A potential cofounder of the included studies is the BDNF genotype of the participant. As some individuals do not have the BDNF genotype (~30% in the general population) (Shiner et al., 2016), it can be assumed that the dose relationship with exercise may be limited. Several confounders of BDNF have been reported including depression and race (Nettiksimmons et al., 2014). Additional natural variation in basal BDNF concentrations is expected due to variations in weather (Molendijk et al., 2012), age, weight, and phase of menstrual cycle (Begliuomini et al. 2007). These variables will be recorded and accounted for when the provided venous blood samples collected at various time points are analysed. Of the 17 included studies in this systematic review and meta-analysis, only one study (5%) reported BDNF genotype (Chang et al., 2019).

5.6.2 Future directions

To optimise the clinical implications of research results, future studies must provide sufficient detail to allow clinicians to understand the demographics examined and the specifics of the exercise intervention provided. The use of standardised stroke descriptors such as the NIHSS (Amalia & Dalimonthe, 2020) or Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Adams et al., 1993) to better allow clinicians to identify if their patients are similar to those within the investigated cohort. In addition, BDNF genotype must be tested and reported to allow for increased accuracy in the analysis of BDNF concentration changes following exercise.

The use of the FITT Principle (Pescatello, 2014) and Consensus on Exercise Reporting Template (CERT) 16-point criteria to describe the exercise intervention provided will ensure future studies present adequate detail to facilitate reproducible interventions within clinical practice. This must include any personalisation and fidelity of the interventions (Walker et al., 2017). Aerobic exercise is already recommended as part of multi-disciplinary stroke

rehabilitation to improve cardiorespiratory health and fitness (Billinger et al., 2014), and reduce the risk of stroke (Lee et al., 2003). Therefore, high intensity aerobic exercise must be considered as an important part of any stroke rehabilitation program, and its use in close temporal proximity to other therapy modalities may be recommended due to the positive benefits demonstrated in the literature (Thomas et al., 2017). Future studies must explore the optimal dose and temporal ordering of high intensity aerobic exercise as an adjunct therapy modality to optimise motor re-learning and functional improvements post-stroke.

5.7 Conclusions

The findings of this systematic review suggest that a single session, and program, of high intensity aerobic exercise increases blood-derived BDNF concentration. Additionally, non-aerobic exercise programs may increase blood-derived BDNF concentrations, though the non-significant result and low-degree of homogeneity of the included studies suggest these results should be interpreted with caution. While aerobic exercise is currently recommended as a part of multidisciplinary rehabilitation to promote cardiovascular benefits, the inclusion of high intensity aerobic exercise shows promise as an intervention that may enhance circulating BDNF.

5.8 Implementation of this evidence in this program of research

While this systematic review is a combination of randomised controlled trials (RCTs) and cohort studies (Level 1A and 2A evidence) (Burns et al., 2011), the low and moderate risk of bias identified in the included studies (Sterne et al., 2016; Sterne et al., 2019) does not downgrade this evidence. This systematic review and meta-analysis identified that a single session, and program, of high intensity aerobic exercise produced the largest increases in BDNF concentration post-stroke. However, this increase was slightly larger following a program of high intensity aerobic exercise. One of the largest increases observed when comparing baseline to post-intervention BDNF concentrations was following HIIT (Kim et al., 2019). This intervention is considered safe and feasible for stroke survivors (Crozier et al., 2018; Gibala et al., 2012; Gjellesvik et al., 2021) and is recommended for this population to increase cardiorespiratory fitness and function (Crozier et al., 2018; Gibala et al., 2012). Therefore, high intensity aerobic exercise will be provided in the intervention used in studies 2 and 4 within this program of research due to the health and neuroplastic benefits.

To improve the implementation of this type of exercise in stroke rehabilitation, perspectives of high intensity aerobic exercise will be explored through a mixed method study (Study 2) of this program of research due to the possible benefits offered if undertaken post-stroke.

Chapter 6 STUDY 2: HIGH INTENSITY INTERVAL TRAINING POST-STROKE (HIIT-POST): STROKE SURVIVORS' AND HEALTH PROFESSIONALS' VIEWS

6.1 Preface

Aerobic exercise is strongly recommended post-stroke to improve cardiovascular health, walking efficiency (Billinger et al., 2014), and brain health (Wrann et al., 2013) while reducing secondary stroke risk (Billinger et al., 2014). Current Australian and New Zealand Living Guidelines for Stroke Management recommend moderate intensity continuous aerobic exercise (Stroke Foundation, 2022). But there is emerging evidence supporting the use of HIIT after stroke (Crozier et al., 2018). HIIT, a form of aerobic exercise, involves periods of high intensity aerobic exercise interspersed with periods of lower intensity aerobic exercise (Gibala et al., 2012). Proposed benefits of HIIT for people with stroke include increased ventilatory threshold, walking economy, balance (Wiener et al., 2019) and enhanced neuroplasticity-associated motor learning and functional recovery (Crozier et al., 2018). However, acceptability of HIIT to people with stroke and feasibility to health professionals is unclear. Exploring the clinical utility of HIIT, as well as explicit barriers and facilitators to HIIT after stroke is necessary to optimise participant adherence to the intervention (Simpson et al., 2011) and the development of best practice guidelines that can be applied in clinical settings (Doyle et al., 2013).

A mixed methods approach, including an online questionnaire and semi-structured interview, was used to explore the views of people with stroke and health professionals who work with people with stroke to provide insight into how HIIT might be optimised in clinical settings. Questionnaires were co-designed by the research team and lived experts, incorporating questions targeting barriers and facilitators to HIIT after stroke (Singleton & Straits, 2010). Social media, including academic and personal platforms, were used to distribute the questionnaire to make it accessible to a large participant cohort (Dillman et al., 2014). Semi-structured interviews were conducted with interested participants to elaborate on their perspectives and personal experience of HIIT after stroke.

6.2 Abstract

Objective. To identify perceived barriers and facilitators to the participation in, and recommendation of, HIIT post-stroke from the perspectives of people with stroke and health professionals, respectively.

Methods*.* People with stroke and health professionals who work with people with stroke in Australia were invited to participate in an online questionnaire. Frequency of responses were calculated and presented as counts and percentages. Participants were further invited to participate in a one-on-one online semi-structured interview. Data were analysed using the Framework Analysis approach to identify key themes raised.

Results. Twenty-six people with stroke (mean ± SD 49.2 ± 60.6 months post-stroke, 57.7% female) and 37 health professionals (one basic physician trainee, 12 exercise physiologists and 20 physiotherapists) completed the questionnaire. Ten people with stroke (four female) and eight health professionals (two exercise physiologist, six physiotherapists) participated in a semi-structured interview. Aerobic exercise was not always considered a top priority after stroke. Main barriers to participation in HIIT reported by people with stroke included a lack of knowledge about the benefits of HIIT, a lack of support from other people with stroke and health professionals, and use of the term 'high intensity'. Main facilitators to participation in HIIT reported by people with stroke included education about safety and benefits of HIIT, as well as referral to health professionals who could facilitate participation in HIIT. Main barriers to the recommendation of HIIT reported by health professionals included a lack of knowledge of what to prescribe and when to prescribe HIIT post-stroke, the motivation of the person with stroke, and minimal use of evidence-based HIIT recommendations. Main facilitators to the recommendation of HIIT reported by health professionals included increased education of HIIT prescription and benefits, supervision of participants and appropriate screening prior to commencement, including obtaining medical clearance.

Conclusions. People with stroke and health professionals who work with people with stroke consider HIIT to be a beneficial intervention for use in stroke rehabilitation. Education relating to intervention protocols and participant safety procedures should be provided to people with stroke and health professionals to optimise clinical application.

6.3 Introduction

Reduced participation in physical exercise is one of the strongest predictors of future stroke (Ahangar et al., 2018; Boehme et al., 2017; Gallanagh et al., 2011; Grysiewicz et al., 2008; O'Donnell et al., 2010; Turan et al., 2017). Many people with stroke do not adhere to exercise recommendations, creating a negative cycle of deconditioning associated with decreased function and increased risk of cardiovascular events (e.g., secondary stroke) (Gaskins et al., 2019). Reduced participation in exercise is also associated with poor heart health and cardiovascular function (Gallanagh et al., 2011). Exercise is recommended as part of comprehensive stroke recovery (MacKay-Lyons et al., 2020) and secondary stroke prevention (Gaskins et al., 2019). Aerobic exercise is recommended to promote cardioprotective benefits to reduce the risk of cardiovascular events, including subsequent stroke (Billinger et al., 2014). In particular, high intensity aerobic exercise (RPE 14-17/20) (Liguori et al, 2021) may reduce the risk of stroke by approximately 27% (Lee et al., 2003).

HIIT, which is characterised by alternating bouts of high and low intensity aerobic exercise (Gibala et al., 2012), is deemed safe to integrate into stroke rehabilitation (Crozier et al., 2018; Gjellesvik et al., 2021). To further ensure participant safety during HIIT medical clearance (Mack, 2016) and the completion of an exercise test is recommended prior to commencement (MacKay-Lyons et al., 2020). No serious adverse events have been reported for people with stroke participating in HIIT (Boyne et al., 2016; Boyne et al., 2023; Crozier et al., 2018; Gjellesvik et al., 2021), however individuals included in these studies were appropriately screened for time post-stroke, cardiovascular health, and mobility levels (Boyne et al., 2016; Boyne et al., 2023; Crozier et al., 2018; Gjellesvik et al., 2021). HIIT has been demonstrated to increase the concentration of neurotrophins within the body associated with increased neuroplasticity (Crozier et al., 2018) which may facilitate improved functional outcomes (Nepveu et al., 2017). Reductions in motor impairment, increased functional independence (Billinger et al., 2014; Gjellesvik et al., 2021; Gjellesvik et al., 2012), and improvements in QoL (MacKay-Lyons et al., 2020) are associated with regular participation in exercise post-stroke.

Adherence to regular exercise post-stroke is low (Fini et al., 2017; Gaskins et al., 2019). This may be attributed to an array of factors including mood, motivation, finances, and support

(Fini et al., 2021). Barriers such as motor impairments, fatigue (Débora Pacheco et al., 2021), lack of social support (Aguiar et al., 2022), low exercise self-efficacy (Simpson et al., 2011), and fear of injury or damaging health (Nicholson et al., 2013; Nicholson et al., 2017) are commonly reported barriers to exercise participation by people with stroke. Appropriate education for medical and allied health professionals regarding prescription of safe exercise interventions is recommended as a facilitator to participation and adherence by people with stroke (Fini, Bernhardt, Said, et al., 2021). It has also been suggested that support from qualified professionals, education about the benefits of exercise (Simpson et al., 2011), increased social support, and engagement in activities enjoyed prior to stroke (Nicholson et al., 2014) may assist in overcoming these barriers to participation.

Barriers to exercise prescription experienced by health professionals include lack of self-efficacy (Gaskins et al., 2021; Moncion et al., 2020), inability to supervise exercise, lack of suitable equipment (Condon et al., 2018), unfamiliarity with post-stroke exercise guidelines, and the belief that aerobic exercise is a low priority (Moncion et al., 2020). It has been suggested that the use of evidence-based guidelines of screening and prescription, appropriate monitoring of participants, and education to health professionals is needed to overcome these barriers to exercise prescription for people with stroke (Moncion et al., 2020). However, it is unclear if these barriers and facilitators are applicable to HIIT, or if others exist. This study aims to identify perceived barriers and facilitators to participation in, and recommendation of HIIT post-stroke from the views of people with stroke and health professionals, respectively.

6.4 Methods

An exploratory cross-sectional mixed-methods study design was used to gain insight into the views of HIIT after stroke using a co-designed questionnaire and semi-structured interview. Ethics approval was obtained from ACU HREC (2022-2702H).

6.4.1 Participants

People with stroke and health professionals who work with people with stroke were recruited for this study. Participants were recruited via social media (e.g., Facebook,

LinkedIn, Twitter/X) and via the personal and professional networks of the research team. A detailed explanation of the inclusion criteria and the recruitment method for this study are outlined in Chapter 4.2 Participants and Chapter 4.4 Recruitment.

6.4.2 Measures

All participants were required to complete the online questionnaire via REDCap and/or the semi-structured interview on Zoom as outlined in Chapter

4.6.1 Procedure. In summary, the questionnaire included closed and Likert-type style questions to collect information about exercise habits as well as barriers and facilitators to participation in HIIT by people with stroke. Closed and Likert-type style questions were also used in the health professional questionnaire to collect information about current understanding of the recommendations of exercise post-stroke as well as barriers and facilitators to the recommendation of HIIT post-stroke. The semi-structured interview comprised open-ended questions to explore the participants' perceptions of exercise, and particularly HIIT, after stroke.

6.4.3 Data analysis

Questionnaire data were entered into REDCap by the participant, downloaded, and imported into SPSS for analysis (IBM SPSS Statistics, version 29.0.1.0). Demographic data of the participants are presented as mean and standard deviation, and percentages where appropriate. Questionnaire responses are presented as frequency and percentage. Semi-structured interview data were analysed by two independent assessors using the Framework Analysis approach, presented as themes and subthemes. Interview quotes provided by people with stroke are reported with the acronym PwS and quotes by health professionals are reported as HP. Additional information regarding the methods of data analysis of this study are outlined in Chapter 4.6.2 Data analysis.

6.5 Results

6.5.1 Questionnaire

6.5.1.1 People with stroke

Participants

Twenty-six people with stroke completed the full online questionnaire between 28 March 2023 to 14 September 2023. On examination of the records created in REDCap, 40 people consented to participate, 32 people commenced the questionnaire and 6 people started but did not complete the full questionnaire. Thus, 26 people post-stroke were included in the analysis of barriers and facilitators to HIIT. Participant demographic information is presented in Table 6-1. In summary, participants were several years post-stroke (mean 49.23 ± 60.66 months), most participants were female (57.7%), and most participants experienced at least one impairment after stroke (84.6%).

Of the 26 participants who completed the questionnaire, 15 respondents (57.7%) reported enjoyment with exercise after stroke, with the main reasons for exercise being to improve their health (n = 12, 46.2%), and mobility (n = 8, 30.8%), and to prevent another stroke (n = 3, 11.5%). Of the 26 participants, 50% of respondents reported completing HIIT in the past (i.e., either before or after stroke), and 73.1% (n = 19) of respondents reported interest in HIIT post-stroke.

Table 6-1 People with stroke participant demographics

	Respondents (n = 26)
Time post-stroke (months)	49.23 ± 60.66 (range; 1 – 204)
Age (years)	
18 – 29	1 (3.8)
30 – 39	2 (7.7)
40 – 49	4 (15.4)
50 – 59	5 (19.2)
60 – 69	5 (19.2)
70 – 79	9 (34.6)
Sex	
Male	11 (42.3)
Female	15 (57.7)
Aboriginal and/or Torres Strait Islander	0 (0)
Current impairments post-stroke*	
Walking ability	10 (38.5)
Arm use	10 (38.5)
Memory	8 (30.8)
Communication	4 (15.4)
Fatigue	16 (61.5)
No impairment	4 (15.4)
Use of a walking aid	
Inside and outside	2 (7.7)
Outside only	3 (11.5)
Long distance only	1 (3.8)
Never	20 (76.9)

Note: Values are mean ± standard deviation or frequency (percentage). * Participants could select more than one impairment.

Barriers to HIIT

Table 6-2 reports people with stroke's responses to the barriers to participation in HIIT presented in the co-designed questionnaire. The 'strongly agree' and 'agree' responses

were collated into the agree category, and the 'strongly disagree' and 'disagree' responses were collated into the disagree category. The main barriers to HIIT reported by respondents were related to minimal support from health professionals and other people with stroke, and a lack of knowledge of why HIIT would be beneficial post-stroke.

Table 6-2 People with stroke reported barriers to HIIT

	Respondents n (%)		
	Agree	**Maybe**	**Disagree**
Fear of making health worse	6 (23.1)	3 (11.5)	17 (65.4)
Fear of falling	6 (23.1)	7 (26.9)	13 (50)
Pain	7 (26.9)	4 (15.4)	15 (57.7)
HIIT sounds too hard	3 (11.5)	6 (23.1)	17 (65.4)
Lack of motivation	3 (11.5)	4 (15.4)	19 (73.1)
Discomfort or embarrassment	3 (11.5)	3 (11.5)	20 (76.9)
Fatigue stops participation in HIIT	6 (23.1)	4 (15.4)	16 (61.5)
Impairments post-stroke	5 (19.2)	8 (30.8)	13 (50)
HIIT is a low priority	4 (15.4)	5 (19.2)	17 (65.4)
Lack of time	1 (3.8)	7 (26.9)	18 (69.2)
No space to do HIIT	1 (3.8)	4 (15.4)	21 (80.8)
No equipment to do HIIT	4 (15.4)	7 (26.9)	15 (57.7)
No exercise professional to supervise HIIT	2 (7.7)	4 (15.4)	20 (76.9)
Lack of knowledge about HIIT	5 (19.2)	3 (11.5)	18 (69.2)
Lack of knowledge of the benefits of HIIT	11 (42.3)	6 (23.1)	9 (34.6)
No support from health professionals	19 (73.1)	0 (0)	7 (26.9)
No support from family or friends	1 (3.8)	3 (11.5)	22 (84.6)
No support from other stroke survivors	19 (73.1)	2 (7.7)	5 (19.2)

Abbreviations – HIIT: High Intensity Interval Training.

Additional barriers to exercise reported by the people with stroke in the free text box of the questionnaire are presented in Table 6-3. These additional barriers reinforce the need for information about HIIT and its benefits to promote engagement following stroke.

Table 6-3 Additional barriers to HIIT reported by people with stroke

	Number of participants reporting the barrier
Cons outweigh the benefits of HIIT	1
HIIT may cause fatigue	2
Wouldn't know what to do on their own	1
Current health conditions (e.g., pain, BP)	3
Heart rate limited by medical practitioner	2
Vision concerns	1
Balance concerns	1
Mobility concerns	1

Abbreviations – BP: Blood pressure, High Intensity Interval Training.

Facilitators to HIIT

Table 6-4 reports the people with stroke's responses to the facilitators to HIIT presented in the co-designed questionnaire. The 'strongly agree' and 'agree' responses were collated into the agree category, and the 'strongly disagree' and 'disagree' responses were collated into the disagree category. Facilitators to HIIT reported by respondents were related to the supervision of HIIT by trained professionals and the provision of information about the safety, benefit, and personalisation of the HIIT program.

Table 6-4 People with stroke reported facilitators of HIIT

	Respondents n (%)		
	Agree	**Maybe**	**Disagree**
Trained professional supervision	18 (69.2)	4 (15.4)	4 (15.4)
Knowledge it was safe	22 (84.6)	2 (7.7)	2 (7.7)
Meet other stroke survivors	13 (50)	4 (15.4)	9 (34.6)
Involvement of family and friends	10 (38.5)	4 (15.4)	12 (46.2)
Facilitate mental and physical improvement	23 (88.5)	1 (3.8)	2 (7.7)
Facilitate return to pre-stroke activities	23 (88.5)	1 (3.8)	2 (7.7)
Improved stroke recovery	23 (88.5)	1 (3.8)	2 (7.7)
HIIT was personalised to capacity and goals	23 (88.5)	1 (3.8)	2 (7.7)
HIIT was completed at home	18 (69.2)	3 (11.5)	5 (19.2)
HIIT was completed via telehealth	14 (53.8)	6 (23.1)	6 (23.1)
Shorter sessions to fit schedule	13 (50)	6 (23.1)	7 (26.9)

Abbreviations – HIIT: High Intensity Interval Training.

Additional facilitators to HIIT participation reported by the people with stroke in the free text box of the questionnaire are presented in Table 6-5. The need for objective assessment to identify improvements following a HIIT program are needed to further motivate participants to engage with this modality of exercise training.

Table 6-5 Additional facilitators of HIIT reported by people with stroke

	Number of participants reporting the facilitator
Weight loss	1
Previous experience with HIIT post-stroke	1
Social interaction	1
Measurable improvements	2
Rebuilding brain networks	1

Abbreviations – HIIT: High Intensity Interval Training.

6.5.1.2 Health professionals

Participants

Thirty-seven health professionals completed the online questionnaire between 28 March 2023 to 14 September 2023. On examination of the records created in REDCap, 48 people consented to participate. Of these, 44 participants commenced the questionnaire and 7 participants started but did not complete the full questionnaire. Demographic information is presented in Table 6-6. In summary, most participants were physiotherapists (59.5%), held a master degree or higher in their chosen profession (59.4%) and have been working in their profession for one year or more (97.3%). Twenty-seven (73%) respondents reported they recommend and/or prescribe HIIT to people with stroke, and 23 (62.2%) respondents reported confidence in their ability to prescribe HIIT.

Table 6-6 Health professional participant demographics

	Respondents (n = 37)
Profession	
Physiotherapist	22 (59.5)
Exercise Physiologist	12 (32.4)
Allied Health Assistant	1 (2.7)
Basic Physician Trainee	1 (2.7)
Clinical Nurse Educator	1 (2.7)
Highest degree earned	
Certificate	1 (2.7)
Bachelor degree	11 (29.7)
Graduate diploma	3 (8.1)
Master degree	16 (43.3)
Doctorate	6 (16.2)
Years of experience	
<1 year	1 (2.7)
1-5 years	12 (32.4)
5-10 years	10 (27.1)
10+ years	14 (37.8)
Phase/s of stroke recovery worked with*	
Hyperacute (0 – 24 hours)	4 (10.8)
Acute (1 – 7 days)	8 (21.6)
Early subacute (7 days – 3 months)	22 (59.5)
Late subacute (3 – 6 months)	26 (70.3)
Chronic (>6 months)	30 (81.1)

Note: Values are frequency (percentage). * Participants could select more than one phase of recovery.

Abbreviations – <: Less than, >: More than.

Barriers to HIIT

Table 6-7 reports health professionals' responses to the barriers to the recommendation and/or prescription of HIIT to people with stroke presented in the questionnaire. The 'strongly agree' and 'agree' responses were collated into the agree category, and the

'strongly disagree' and 'disagree' responses were collated into the disagree category. The main barriers to recommending and/or prescribing HIIT reported by respondents were related to a lack of knowledge regarding what to prescribe and when to prescribe HIIT post-stroke, as well as the motivation of the person with stroke.

Table 6-7 Health professional reported barriers to HIIT

	Respondents n (%)		
	Agree	**Neither agree nor disagree**	**Disagree**
Do not know how to recommend/prescribe	12 (32.4)	3 (8.1)	22 (59.5)
Unsure of personalisation to impairments	17 (45.9)	3 (8.1)	17 (45.9)
Unsure of when to commence after stroke	17 (45.9)	5 (13.5)	15 (40.5)
Unsure of post-stroke benefits	7 (18.9)	3 (8.1)	27 (73)
Benefits do not outweigh risks	5 (13.5)	13 (35.1)	19 (51.4)
Cannot safely provide HIIT in current workplace	5 (13.5)	2 (5.4)	30 (81.1)
Lack of resources in workplace	10 (27)	4 (10.8)	23 (62.2)
Lack of time	5 (13.5)	7 (18.9)	25 (67.6)
HIIT is not a top priority in rehabilitation	3 (8.1)	13 (35.3)	21 (56.8)
Age of participant	13 (35.1)	8 (21.6)	16 (43.2)
Motivation of participant	17 (45.9)	5 (13.5)	15 (40.5)
Fatigue level of participant	15 (40.5)	7 (18.9)	15 (40.5)
Low level of pre-stroke exercise	13 (35.1)	5 (13.5)	19 (51.4)
Lack of support from participants' family or friends	10 (27)	7 (18.9)	20 (54.1)
Lack of support from other health professionals	5 (13.5)	10 (27)	22 (59.5)

Abbreviations – HIIT: High Intensity Interval Training.

Additional barriers to HIIT recommendation and/or prescription reported by health professionals in the free text box of the questionnaire are presented in Table 6-8. Of the 37 respondents, 2 (5.4%) participants of whom were physiotherapists, reported being formally trained in the recommendation and/or delivery of HIIT, undertaken through a professional

development course. Additional barriers reported reinforce the need for in-depth education across the multidisciplinary team to facilitate the optimal use of HIIT.

Table 6-8 Additional health professional reported barriers to HIIT

	Number of participants reporting the barrier
Lack of consistency across the MDT (e.g., exercise professional may prescribe HIIT but a nurse/doctor insinuate the person with stroke should take it easy, or if they feel fatigued after exercise to insinuate they went too hard)	2 1
Concept of a gym as a 'torture chamber'	1
Clinical stability and status	1
Cultural language boundaries	1
Poor health literacy	1
Cardiac comorbidities require medical clearance	2
Other comorbidities may influence the implementation of HIIT	1 1
Previous experience and preferred treatment of the person with stroke	1 1
Time barriers	
Focus on motor retraining takes priority	1
Workplace culture (e.g., many senior therapists focus on more traditional rehabilitation approaches)	
Role does not include exercise prescription (i.e., Allied Health Assistant), but see the benefits of HIIT	

Abbreviations – HIIT: High Intensity Interval Training, MDT: Multidisciplinary team.

Facilitators to HIIT

Table 6-9 reports participants' responses to the facilitators of HIIT presented in the questionnaire. The 'strongly agree' and 'agree' responses were collated into the agree category, and the 'strongly disagree' and 'disagree' responses were collated into the

disagree category. Facilitators to HIIT reported by respondents were related to increased education of HIIT prescription and the benefits of HIIT, supervision of people with stroke during exercise sessions and appropriate screening prior to commencement.

Table 6-9 Health professional reported facilitators of HIIT

	Respondents n (%)		
	Agree	**Neither agree nor disagree**	**Disagree**
Interested to improve knowledge of use of HIIT	32 (86.5)	5 (13.5)	0 (0)
One-on-one supervised sessions	33 (89.2)	2 (5.4)	2 (5.4)
Group HIIT classes	32 (86.5)	4 (10.8)	1 (2.7)
Telehealth sessions with appropriate screening	24 (64.9)	5 (13.5)	8 (21.6)
Medical clearance needed prior to HIIT	21 (56.8)	10 (27)	6 (16.2)
Education on safety of HIIT	28 (75.7)	4 (10.8)	5 (13.5)
Education on benefits of HIIT	33 (89.2)	4 (10.8)	0 (0)
Early commencement to increase adherence	27 (73)	8 (21.6)	2 (5.4)
Greater support from employers	28 (75.7)	6 (16.2)	3 (8.1)
Changing the title of HIIT	18 (48.6)	10 (27)	9 (24.3)

Abbreviations – HIIT: High Intensity Interval Training.

Additional facilitators to exercise reported by the participants in the free text box of the questionnaire are presented in Table 6-10. Additional facilitators included the need for education about testing, prescription, and the supervision of HIIT for people with stroke.

Table 6-10 Additional health professional reported facilitators of HIIT

	Number of participants reporting the facilitator
Implementation of BCTs to change exercise behaviour	1
Cardiopulmonary exercise stress tests/ Appropriate screening	3 1
Work-rest ratio tailored to individual	2
Gradual introduction of HIIT after appropriate screening	1
Increased number of exercise physiologists on inpatient hospital wards	1
Plain language handouts developed by a national body (e.g., Stroke Foundation) for professionals to provide to stroke survivors	1
Toolkit for health professionals	

Abbreviations – BCTs: Behaviour Change Techniques, HIIT: High Intensity Interval Training.

For the question, 'which health professionals should be referred to for the delivery of HIIT post-stroke (i.e., allied health assistant, exercise physiologist, physiotherapist and/or personal trainer)', exercise physiologists were the most reported (n = 35), followed by physiotherapists (n = 28).

6.5.2 Interview

6.5.2.1 Participants

A subset of people with stroke who completed the questionnaire (n = 10) and a group of health professionals who work with people with stroke (n = 8) partook in an individual semi-structured interview with a member of the research team via Zoom. Demographic information for the participants with stroke is presented in Table 6-11. In summary, people with stroke were several years post-stroke (mean 39.3 ± 24.8 months), five participants were female, and most participants report at least one current impairment (90%).

Table 6-11 Interview demographics for people with stroke

	Respondents (n = 10)
Time post-stroke (months)	39.3 ± 24.8 (range; 1 – 81)
Age (years)	
18 – 29	1 (10)
40 – 49	1 (10)
50 – 59	2 (20)
60 – 69	2 (20)
70 – 79	4 (40)
Sex	
Male	5 (50)
Female	5 (50)
Aboriginal and/or Torres Strait Islander	0 (0)
Impairments after stroke*	
Walking ability	3 (30)
Arm use	2 (20)
Memory	3 (30)
Communication	1 (10)
Fatigue	6 (60)
No impairment	1 (1)

Note: Values are mean ± standard deviation or frequency (percentage). * Participants could select more than one impairment.

Demographic information for the included health professionals is presented in Table 6-12. In summary, most health professionals interviewed were Physiotherapists (75%), held a master degree in their relevant profession (75%) and worked with people with stroke in the early/late subacute (75%) or chronic (100%) phases of stroke recovery.

Table 6-12 Interview demographics for health professionals

	Respondents (n = 8)
Profession	
Physiotherapist	6 (75)
Exercise Physiologist	2 (25)
Highest degree earned	
Bachelor degree	2 (25)
Master degree	6 (75)
Years of experience	10.5 ± 6.3
Phase/s of stroke recovery worked with*	
Acute (1 – 7 days)	2 (25)
Early subacute (7 days – 3 months)	2 (25)
Late subacute (3 – 6 months)	4 (50)
Chronic (>6 months)	8 (100)

Note: Values are frequency (percentage) or mean ± standard deviation. * Participants could select more than one phase of recovery.

Abbreviations - <: Less than, >: More than.

6.5.2.2 Themes

Analysis of interview transcripts revealed six overarching themes relating to the participation in, and prescription of, HIIT after stroke.

Theme 1: Aerobic exercise is not always a priority after stroke.

Subtheme 1: Multidisciplinary approach shifts the priority of therapy sessions.

Participants reported that aerobic exercise was not always considered a top priority after stroke. The use of a multidisciplinary approach (e.g., people with stroke seeing a physiotherapist and an exercise physiologist) was reported to shift the priority of therapy sessions, in particular sessions led by a physiotherapist:

> *"The physio is there by my side, but she's doing the finer stuff. Like the finer detail…what muscles to use. The exercise physiologist puts me on a spin cycle, does a lot of muscle*

training and correct[ing] movement and [stays] by my side. The carer…he was a gym owner, so we do a lot of bush walking and bike riding, lots of different stuff" (PwS3).

"Sometimes I'll [physiotherapist] be seeing them, and an exercise physiologist will be seeing them as well, so that can sort of change where the focus lies" (HP1).

Subtheme 2: Client engagement may shift importance of aerobic exercise after stroke.

Health professionals reported that the importance they place on aerobic exercise in stroke rehabilitation is often influenced by the engagement of the person with stroke:

"In a way, feels like a lower priority in their mind, even though we know it's important" (HP3).

"People don't want a bar of it in my experience, unfortunately" (HP6).

Subtheme 3: Functional recovery takes priority after stroke.

It is considered that functional recovery takes priority over aerobic exercise in stroke rehabilitation, as reported by the health professionals interviewed:

"Sometimes you don't get to it, almost because there's so much else happening" (HP1).

"If they're struggling with something that's really stopping them from performing their daily living, then that might take higher precedence" (HP7).

One participant reported concern that if the health professional does not prioritise functional training, the person with stroke may find another therapist who will:

"What are their priorities and how can I get them to engage with me as a therapist? Sitting down and saying, 'Let's do some cardiovascular fitness', people may go, 'No thanks, I'll find a physio who will look at my hand or look at my weak ankle'…gotta be really selective" (HP6).

Theme 2: High Intensity Interval Training is beneficial after stroke.

Subtheme 1: Physical benefits of HIIT.

People with stroke and health professionals voiced that they consider HIIT to be beneficial during stroke recovery. HIIT was thought to be able to facilitate physical benefits for people with stroke including improvements in fitness, physiological improvements (e.g., cardiovascular benefits), and secondary stroke prevention:

> *"I want to reduce my risk of having a stroke for other health reasons in the future" (PwS4).*

> *"Because of my fitness, it also makes bike riding easier because I'm fitter and stronger" (PwS10).*

> *"There's increased blood supply…also the heart health and the systemic improvements. So I don't think there's anything bad about it, apart from a bit of hard work" (HP2).*

> *"…changing what's happening at the muscular cellular level, which could then possibly transfer to the client's ability to walk a little bit quicker or climb stairs easier" (HP7).*

Subtheme 2: Other benefits of HIIT.

People with stroke and health professionals reported that HIIT could have potential benefits for mental health after stroke, including promoting neuroplasticity and mood:

> *"If I thought it was affecting my brain, neurogenesis, I would definitely [do it]. It's a powerful thing to think about" (PwS1).*

> *"I'm not very good on the right side, but if I do high intensity, I think it might speed up the nervous system (PwS2).*

> *"I think it's really important for mental health…and…mood, which is another thing about stroke" (HP6).*

Theme 3: Varied use of High Intensity Interval Training after stroke.

Subtheme 1: People with stroke are interested in HIIT.

People with stroke were interested in participating in HIIT, however health professionals voiced that not all people with stroke were wanting to participate in HIIT:

> *"I want my body and mind to be as physically healthy as it can be" (PwS4).*
>
> *"I'd be willing to do it" (PwS10).*
>
> *"I've seen people who actually don't even want to try it, or I have people on the other end that want to do everything and say, 'Work me very hard, very hard, I want to get better'" (HP3).*

Subtheme 2: Limitations in the use of HIIT by health professionals after stroke.

Health professionals highlighted that the use of HIIT in clinical practice is varied, largely due to logistical issues and potential prejudices about the clinician:

> *"It depends on the setting; it depends on the equipment I've got. If I have a physio[therapy] student who's happy to sit with the patient for the whole time, I'll definitely do it" (HP4).*
>
> *"We have a lot of younger…male clinicians who are quite athletic who I actually think would not be opposed to the idea" (HP2).*

Subtheme 3: Barrier – HIIT should not commence until participant is medically stable.

Health professionals reported that medical clearance should be obtained prior to the commencement of HIIT after stroke. Health professionals voiced that this would enable people with stroke to access HIIT as early in the stroke recovery process as was deemed safe for the individual to participate:

> *"There would be a 'this is too early point'…if they're not medically stable. And I think that would be a barrier" (HP1).*
>
> *"If they've got doctor's clearance and they're safe to do it, then they can start whenever" (HP5).*

People with stroke did not voice concerns regarding their medical stability as a barrier to participation in HIIT.

Subtheme 4: Facilitator – Medical clearance should be obtained to commence HIIT after stroke.

Health professionals expressed that obtaining medical clearance prior to commencing HIIT would increase their confidence in the safety of this intervention after stroke. The importance for medical clearance was greater for individuals early post-stroke and who present with comorbidities:

> *"I think [the time to start HIIT post-stroke] depends on how far down the track they are. Obviously, the more acute they are, then yes [medical clearance is needed]" (HP7).*

> *"If there's risk factors, or if there is anything in like medical history, I will [get medical clearance] just to be safe" (HP1).*

Two participants did report concerns about the knowledge of HIIT understood by medical staff who may provide this clearance:

> *"Even if you say 80% [intensity], they [the GP] forget that it's their [person with stroke] 80%, it's not a blanket 80%. So, I think there's also a disconnect with the medical professionals also understanding that" (HP7).*

> *"Like it [getting medical clearance] would make me feel so much better…my only concern with that is who's going to be giving the medical clearance?...Like if that's going to be the GP giving medical clearance then…I do not trust on their ability to know what high intensity interval training is and know that it's safe" (HP8).*

Theme 4: Minimal use of guidelines to prescribe High Intensity Interval Training after stroke.

Subtheme 1: Prescription is not usually based on recommendations of HIIT after stroke.

Health professionals reported the prescription of exercise intensity and/or duration of HIIT intervals were not developed using exercise recommendations or guidelines for stroke

populations. Participants were also unaware of existing HIIT guidelines for people with stroke:

"The short answer is no [did not use guidelines]…I was just going by gut feel" (HP4).

"I don't specifically know what they are [Stroke Foundation guidelines]…I don't think I've ever sought them out" (HP8).

Subtheme 2: Baseline assessments are not used to prescribe exercise intensity.

Health professionals thought that baseline assessments should be conducted prior to starting a HIIT program, however the assessments currently used often did not provide relevant information to prescribe exercise intensity:

"I do all the outcome measures at the start like you Six-Minute Walk Test…but that doesn't really help you work out exercise intensity" (HP1).

"You've gotta do your at least submax[imal] test, so you're getting some type of idea of how they're responding and how they're recovering to an increasing workload" (HP7).

Subtheme 3: Barrier – Lack of formal training on provision of HIIT after stroke.

Health professionals overall reported having received no formal training in the prescription, and delivery, of HIIT for a person with stroke, however many were interested in undertaking this education:

"No I haven't [had formal training]. But…it would be something that I'd be very interested in" (HP3).

"…I engaged in a couple of short PD's [professional developments] that Michael [a colleague] ran. And this wasn't necessarily for any population group, but it was a general review…to create high intensity training intervals" (HP7).

Subtheme 4: Facilitator – Education for health professionals about the use of HIIT after stroke.

Health professionals were interested in obtaining further education about the use of HIIT after stroke, including potential protocols to follow and appropriate screening:

> *"…educate staff about the principles of how to do it…they may think that they need specific equipment where they don't" (HP3).*

> *"The risks versus benefits analysis…type of screening to be done in addition to your typical screening…preferred mode of delivery…common medications that may be contraindicated" (HP7).*

This information could be provided run as a *"professional development"* or a *"presentation as part of an in-service" (HP3).* Participants also reported that this information must be put *"into some guidelines, that's usually where people go first" (HP5).*

Theme 5: Use of the term 'High Intensity Interval Training' after stroke.

Subtheme 1: Barrier – The term 'High Intensity' may be off-putting.

The people with stroke and health professionals interviewed reported the use of the term 'high intensity' may be off-putting to people with stroke. The term was considered intimidating, especially to those people with stroke who were more apprehensive or older:

> *"'High intensity' kind of excludes someone…who thinks that they're a little bit vulnerable" (PwS2).*

> *"To somebody a little bit older they'd be like, 'Oh is this going to hurt?'" (PwS3).*

> *"I think when you say, 'high intensity', the first thing I can see people will just go, 'Do I have to work very hard?'…we've come across people who just went, 'This is too hard, just send me to a nursing home'" (HP3).*

Subtheme 2: Facilitator – Avoid the use of the term 'High Intensity'.

The health professionals interviewed in this study reported the term 'high intensity' should not be used when discussing this intervention with people with stroke. Instead, focus should be placed on the intervals used:

> *"I can't think of many instances. I don't sit down and say, 'Alright, now we're gonna do some high intensity interval training' because I just feel that most of my patients would go. 'You're mad, you've lost the plot'…but I don't sell it to them as that usually" (HP6).*

> *"It might just be worded as 'interval training'. You know…, 'We're working hard for periods, on and off periods…fast and slow'. I don't know that we actually use high intensity interval training" (HP7).*

Two main facilitators to the use of HIIT after stroke, voiced by people with stroke and health professionals interviewed, included access to health professionals to deliver HIIT after stroke and the provision of education about HIIT after stroke.

Theme 6: Access to health professionals to deliver High Intensity Interval Training after stroke.

Subtheme 1: Referral to appropriate health professionals.

Interview participants reported that referral to appropriate health professionals to provide HIIT interventions could increase participation. People with stroke did not express a preferred health profession, however health professionals considered exercise physiologists as the ideal profession. Most health professionals considered a multidisciplinary team approach would be best:

> *"As long as the health professional understood the challenges…with each [person]" (PwS1).*

> *"Having someone, maybe a trainer or a Physio[therapist]…I feel that if you had someone that understood that you might physically be able to do something but mentally your*

mind says no, and they were to be with you and push you out of your comfort zone. But also support you when you fail, then that would be helpful" (PwS4).

"Physiotherapists and Exercise Physiologists can work together…discuss the patients together…" (HP3).

"Interdisciplinary allied health would be invaluable" (HP6).

"I think Exercise Physiologists got more training in terms of how to adapt interval training and progress interval training" (HP7).

Subtheme 2: Monitoring of people with stroke.

People with stroke expressed the need for appropriate monitoring during HIIT sessions could increase participation and prescription:

"Some sort of monitoring…so that I can feel safe" (PwS2).

Health professionals reported the Rating of Perceived Exertion (RPE) scale (Borg, 1970) as the main monitoring strategy utilised in clinical practice:

"The RPE scale would be my main one" (HP1).

"Usually RPE or with blood pressure and a pulse oximeter" (HP8).

Subtheme 3: High Intensity Interval Training needs to be personalised after stroke.

In addition to monitoring, participants reported that HIIT protocols should be individualised to the person with stroke:

"High intensity is different for different people" (PwS5).

Health professionals reported that the severity of the stroke and associated impairments were the main factors to consider when prescribing HIIT after stroke:

"Severity, the amount of assistance they needed and the way the program is set up" (HP3).

"Impairment level. For example, if they're hemiparetic and substantially affected…I'm not expecting them to be able to generate enough power or force at a consistent pace" (HP7).

Theme 7: Provision of education about High Intensity Interval Training after stroke.

Subtheme 1: Education about safety for people with stroke to engage in HIIT.

People with stroke and health professionals identified education as necessary to increase the uptake and prescription of HIIT after stroke. Education for people with stroke should centre around safety for the participant, in particular the safety of the high intensity intervals:

> *"I suppose I'm a bit concerned about the word 'high intensity'…the only thing that scares me a bit is whether it's safe enough for me to do it physically" (PwS1).*
>
> *"I'd have to be very trusting on what people would say and if they said it was good then I'd do it. If I read it back on the on the back of the Kellogg's packet, maybe I'd be a bit dubious" (PwS3).*
>
> *"The only reason for not getting involved was…in terms of the high intensity part of things, is the concern for high blood pressure and having high blood pressure with stroke kind of thing" (PwS5).*
>
> *"…the education is quite important to let people know that this is safe, you can do it" (HP4).*
>
> *"If you're able to give them the information of risk versus benefit" (HP7).*

Subtheme 2: Education about what High Intensity Interval Training entails.

Education for participants must also include information about what HIIT entails, including the meaning of the abbreviation and that 'high intensity' is relative to the participant:

> *"You don't get any information from the acronym…that's what scares me, you don't know what it is" (PwS2).*
>
> *"You just need a bit of an explanation as to what it is" (PwS5).*

"Education it says 'high intensity', but that doesn't mean we're gonna run Mount Everest. What it means is we're just gonna work a little harder than what you can normally do, and that is your Everest" (HP2).

"You never know what they see in social media, Facebook or TikTok or whatever…they might have been misinformed…[health professionals] can explain to them, educate them what it actually involves" (HP3).

<u>Subtheme 3: High Intensity Interval Training provides a challenge/goal.</u>

Some people with stroke perceive HIIT as a challenge or goal to achieve. Similarly, health professionals believe promoting the intervention as a challenge may increase participation:

"To me it would be like, 'Bring it on'…to me it sounds like a goal in itself" (PwS3).

"Make it into a bit of a challenge or add a bit of banter or something like that would maybe make it a bit more engaging" (HP6).

Themes, subthemes and reflective comments from people with stroke and health professionals relating to HIIT are presented in Table 6-13. Themes were also developed pertaining to general exercise after stroke. These included exercise is beneficial, stroke impairments impact exercise after stroke, exercise can increase confidence with exercise and working with health professionals is a facilitator of exercise after stroke. Themes, subthemes, and reflective comments related to general exercise after stroke are presented in Appendix 11.

Table 6-13 Themes, subthemes and reflective comments relating to HIIT after stroke

Theme	Sub-theme	People with stroke (PwS)	Health professionals (HP)
Aerobic exercise is not always a priority after stroke	**Multidisciplinary approach shifts the priority of therapy sessions**	**PwS3:** "The physio is there by my side, but she's doing the finer stuff. Like the finer detail…what muscles to use. The exercise physiologist puts me on a spin cycle, does a lot of muscle training and correct[ing] movement and [stays] by my side. The carer…he was a gym owner, so we do a lot of bush walking and bike riding, lots of different stuff".	**HP1:** "Sometimes I'll [physiotherapist] be seeing them, and an exercise physiologist will be seeing them as well, so that can sort of change where the focus lies". **HP3:** "I don't think physios address aerobic stuff that much". **HP5:** "And for all my clients in general they usually see an exercise physiologist as well, so they usually cover more so the resistance and the aerobic training". **HP8:** "If they had other healthcare workers, I would try and integrate it with their support worker".
	Client engagement may shift importance of aerobic exercise after stroke		**HP3:** "In a way, feels like a lower priority in their mind, even though we know it's important". **HP4:** "A lot of times they don't feel comfortable that they know that they are able to exercise. I've had people say to me, 'Am I gonna have another stroke as I'm pushing this so hard?'". **HP5:** "Like it's people in general don't place importance on exercise. So whether they've had a stroke or not". **HP6:** "People don't want a bar of it in my experience, unfortunately".
	Functional recovery takes priority after stroke		**HP1:** "Sometimes you don't get to it, almost because there's so much else happening". **HP3:** "Somebody who is a very severe stroke, very disabled, then we're focusing more on sit to stand, sitting balance…compared to someone who had a TIA then we may start focusing on walking straight away". **HP4:** "Depends on their goal". **HP6:** "What are their priorities and how can I get them to engage with me as a therapist? Sitting down and saying, 'Let's do some cardiovascular fitness', people may go, 'No thanks, I'll find a physio who will look at my hand or look at my weak ankle'…gotta be really selective". **HP7:** "If they're struggling with something that's really stopping them from performing their daily living, then that might take higher precedence".

HIIT is beneficial after stroke	**Physical benefits of HIIT**	**PwS2:** "I know that it [HIIT] would potentially help me, especially so early after this stroke". **PwS4:** "I want to reduce my risk of having a stroke for other health reasons in the future". **PwS6:** "I sort of feel like the chances are I could probably improve my fitness further". **PwS10:** "Because of fitness, it also makes bike riding easier because I'm fitter and stronger".	**HP2:** "There's increased blood supply that would definitely be beneficial…also the heart health and the systemic improvements. So I don't think there's anything bad about it [HIIT], apart from a bit of hard work". **HP4:** "In a shorter amount of time you can have greater aerobic gains". **HP5:** "It's good for your cardiovascular system…help prevent you from having a future stroke". **HP7:** "Not just the cardiovascular response, but also then changing what's happening at the muscular cellular level, which could then possibly transfer to the client's ability to walk a little bit quicker or climb stairs easier".
	Other benefits of HIIT	**PwS1:** "If I thought it was affecting my brain, neurogenesis, I would definitely. It's powerful thing to think about". **PwS2:** "I'm not very good on the right side, but if I do high intensity, I think that might speed up the nervous system".	**HP1:** "I guess even just like mental health improvements…potentially cognition improvements". **HP4:** "…it'll probably be more interesting". **HP5:** "It's good for brain health, neuroplasticity". **HP6:** "I think it's really important for mental health…and…mood which is another thing about stroke".
Varied use of HIIT after stroke	**People with stroke are interested in HIIT**	**PwS4:** "I want my body and mind to be as physically healthy as it can be". **PwS6:** "Your physical health, your mental health, social interaction. All of them are part and parcel of how you manage post-stroke". **PwS10:** "I'd be willing to do it".	**HP3:** "I've seen people who actually don't even want to try it, or I have people on the other end that want to do everything and say, 'Work me very hard, very hard, I want to get better'". **HP6:** "I have a period of time where people are much more open…then periods of time where I feel like every patient is telling me to bugger off and they're not interested".
	Limitations in the use of HIIT by health professionals after stroke		**HP2:** "Very limited". "We have a lot of younger sort of male clinicians who are quite athletic who I actually think would not be opposed to the idea". **HP4:** "It depends on the setting; it depends on the equipment I've got. If I have a physio student who's happy to sit with the patient for the whole time, I'll definitely do it".
	Barrier: HIIT should not commence until participant is medically stable		**HP1:** "There would be a 'this is too early point'…if they're not medically stable. And I think that would be a barrier to starting". **HP2:** "I think the sooner the better if it's deemed safe".

			HP5: "If they've got doctor's clearance and they're safe to do it, then they can start whenever".
Varied use of HIIT after stroke	**Facilitator: Medical clearance should be obtained to commence HIT after stroke**		**HP1:** "If there's risk factors, or if there is anything in like medical history, I will [get medical clearance] just to be safe". **HP3:** "You get the green light from the medicos, then why can't we start sooner?". **HP4:** "But if you've got someone who's got like a whole list of comorbidities, and they're coming in and they just don't look well…you get this gut feeling like I think you need medical clearance for this". **HP7:** "I think [the time to start HIIT post-stroke] depends on how far down the track they are. Obviously, the more acute they are, then yes [medical clearance is needed]". "Even if you say 80% [intensity], they [the GP] forget that it's their [person with stroke] 80%, it's not a blanket 80%. So, I think there's also a disconnect with the medical professionals also understanding that". **HP8:** "Like it [getting medical clearance] would make me feel so much better…my only concern with that is who's going to be giving that medical clearance?...Like if that's going to be the GP giving medical clearance then…I do not trust on their ability to know what high intensity interval training is and know that it's safe".
Minimal use of guidelines to prescribe HIIT after stroke	**Prescription is not usually based on recommendations of HIIT after stroke**		**HP1:** "Based on, I guess, ability to achieve it". **HP3:** "The American Sports Association…Google…I'll go and do a literature review, look for RCTs or systematic reviews". **HP4:** "The short answer is no [did not use guidelines]…I was just going by gut feel". **HP8:** "I don't know specifically what they are [Stroke Foundation guidelines]…I don't think I've ever sought them out".
	Baseline assessments are not used to prescribe exercise intensity		**HP1:** "I do all the outcome measures at the start like your Six-Minute Walk Test…but that doesn't really help you work out exercise intensity". **HP2:** "Generally speaking, it's just more the RPE and we would then monitor…outcome through the Six-Minute Walk Test".

			HP4: "Before I prescribe aerobic stuff, I do a Six-Minute Walk Test or something like that to gauge what their capacity is from an aerobic point of view". **HP7:** "You've gotta do your at least submax[imal] test, so you're getting some type of idea of how they're responding and how they're recovering to an increasing workload".
Minimal use of guidelines to prescribe HIIT after stroke	**Barrier: Lack of formal training on provision of HIIT after stroke**		**HP1:** "Not as such…I wouldn't say I have". **HP3:** "No I haven't. But I mean it would be something that I'd be very interested in". **HP7:** "I'm going to yes, only because I engaged in a couple of short PD's that Michael [colleague] ran. And this wasn't necessarily for any population group, but it was a general review…to create high intensity training intervals".
	Facilitator: Education for health professionals about the use of HIIT after stroke		**HP2:** "You have to be on board with it yourself and then your client's going to be on board". **HP3:** "Educating the staff that yes, we need to address fitness…educate staff about the principles of how to do it. Because…they might think that they need specific equipment where they don't. "Run professional development…deliver the presentation as part of an inservice". **HP5:** "If you get into some guidelines, that's usually where people go to first". **HP6:** "I think perhaps I feel like it could be something that could be delivered via Zoom…in person would certainly be more engaging". **HP7:** "The risks versus benefits analysis…type of screening to be done in addition to your typical screening…preferred mode of delivery…common medications that may be contraindicated".
Use of the term 'High Intensity Interval Training' after stroke	**Barrier: The term 'High Intensity' may be off-putting**	**PwS1:** "For those who are more sedate about it, it might be a bit much. You might have to have stages or something like that". **PwS2:** "'High intensity' kind of excludes someone…who thinks that they're a little bit vulnerable". **PwS3:** "To somebody a little bit older they'd be like, 'Oh is this	**HP3:** "I think when you say, 'high intensity', the first thing I can see people will just go, 'Do I have to work very hard?'. Because some people, even though they want to get better, we've come across people who just went, 'This is too hard, just send me to a nursing home'". **HP6:** "I think that I would find for a lot of patients…it's

		going to hurt?'". **PwS5:** "I can see why it would put people off to be honest".	intimidating". **HP7:** "It sounds intimidating".
Use of the term 'High Intensity Interval Training'	**Facilitator: Avoid the use of the term 'High Intensity'**		**HP5:** "'We're doing high interval training. We're just gonna do some interval exercises where you work real quick and then you rest for a little bit and then we go again". **HP6:** "I can't think of many instances. I don't sit down and say, 'Alright, now we're gonna do some high intensity interval training' because I just feel that most of my patients would go. 'You're mad, you've lost the plot'…but I don't sell it to them as that usually". **HP7:** "It might just be worded as 'interval training'. You know…, 'We're working hard for periods, on and off periods…fast and slow'. I don't know that we actually use high intensity interval training".
Facilitator: Access to health professionals to deliver HIIT after stroke	**Referral to appropriate health professionals**	**PwS1:** "As long as the health professional understood the challenges…with each [person]". **PwS4:** "But consistently the recommendation was to try and go back to normal life…personally, I think sometimes doctors can be so far removed from anxiety being a real debilitating thing and what a person can be feeling that they don't realise that suggesting going back to normal life doesn't help". "Having someone, maybe a trainer or physio…I feel that if you had someone that understood that you might physically be able to do something but mentally your mind says no, and they were to be with you and push you out of your comfort zone. But also support you when you fail, then that would be helpful".	**HP1:** "A physiotherapist or an exercise physiologist". **HP2:** "Exercise physiologists are probably best suited to deliver it…you guys have better motivational skills". "I think role sharing is really important". **HP3:** "Physiotherapists and exercise physiologists can work together…discuss the patients together because the EP's may not be familiar with the level of assistance or the ability the patient needed". "And the medical team". **HP6:** "Interdisciplinary allied health would be invaluable". **HP7:** "I think we've [exercise physiologists] got more training in terms of how to adapt interval training and progress interval training".
	Monitoring of people with stroke	**PwS2:** "Some sort of monitoring…so that I can feel safe". **PwS3:** "I think that somebody being there, it's not something I'd be able to do myself and its only pure motivation. If somebody was there cracking the whip, I'd do it you know". **PwS5:** "Guiding me in the right direction".	**HP1:** "The RPE scale would be my main one". **HP6:** "Where you start to feel that you can still talk but can't chat to me…you know, can't tell me a story about your weekend instead its more, "Yes or no'". **HP7:** " [more value placed on] RPE". **HP8:** "Usually by RPE or with blood pressure and a pulse oximeter".

	HIIT should be personalised after stroke	**PwS5:** "High intensity is different for different people". **PwS7:** "Train the instructor how to deal with participants who have had a stroke or fatigue".	**HP1:** "It's hard to get that aerobic or that high intensity interval with those guys that are really significantly and severely affected. But I guess with the more mild to moderate stroke survivors, I'd just be saying like, 'Give it a go". **HP3:** "Severity, the amount of assistance they needed and the way the program is set up". **HP7:** "Impairment level. For example, if they're hemiparetic and substantially affected…I'm not expecting them to be able to generate enough power or force at a consistent pace". **HP8:** "Want to make sure the client is doing what they're comfortable with".
Facilitator: Provision of education about HIIT after stroke	**Education about safety for people with stroke to engage in HIIT**	**PwS1:** "I suppose I'm a bit concerned about the word 'high intensity'…the only thing that scares me a bit is whether it's safe enough for me to do it physically". **PwS3:** "Unfortunately…when you have a stroke you're put on a lot of blood medications, so a lot to lower your heart rate. You can't really do high intensity with that, or I haven't found a way without fainting". "I'd have to be very trusting on what people would say and if they said it was good then I'd do it. If I read it back on the on the back of the Kellogg's packet, maybe I'd be a bit dubious,". **PwS4:** "I had a lot of anxiety then around exercising and actively causing my body to be out of breath". "The level of intensity was still low, due to the intense fatigue I was feeling after exercising and in turn that fatigue could trigger anxiety or a panic attach, and I was again still not ready to push myself out of my comfort zone". **PwS5:** "The only reason for not getting involved was…in terms of the high intensity part of things, is the concern for high blood pressure and having high blood pressure with stroke kind of thing".	**HP1:** "It's the safety stuff, the purpose of why we're doing it". **HP4:** "I think education is quite important to let people know that this is safe, and you can do it". **HP7:** "If you're able to give them the information of risk versus benefit".
	Education about what HIIT entails	**PwS2:** "You don't get any information from the acronym…that's what scares me, you don't know what it is". **PwS4:** "I just don't know what it is. It's a fear of if I do that little intensive spurt I'm gonna crash and burn. So it's probably more the unknown".	**HP2:** "Education it says 'high intensity', but that doesn't mean we're gonna run Mount Everest. What it means is we're just gonna work a little harder than what you can normally do, and that is your Everest". **HP3:** "Who knows what they see in social media, Facebook or

		PwS5: "Doesn't actually convey the best kind of thing, unless you're boxing maybe". "You just need perhaps a bit of an explanation as to what it is".	TikTok or whatever…they might have been misinformed…[health professionals] can explain to them, educate them what it actually involves". "Educate them [participants] overall on the HIIT principle, but also [that it is] personalised. So it's related back to why it's relevant to them". **HP8:** "Relative high intensity".
Facilitator: Provision of education about HIIT after stroke	**HIIT provides a challenge/goal**	**PwS1:** "I love it personally…love the challenge of it". "I was already doing exercise so that helped. And that's why I have a latent interest in encouraging this sort of thing". **PwS3:** "To me it would be like, 'Bring it on'". "To me it sounds like a goal in itself…I'm happy because I'm goal-oriented".	**HP6:** "Make it into a bit of a challenge or add a bit of banter or something like that would maybe make it a bit more engaging". "I just ease people into it and say, 'Well, today let's try where we just work for a little period of time a bit more. You give it a bit more, and then the bonus is you get a little active rest…".

6.6 Discussion

HIIT is currently not a routine component of stroke rehabilitation, as voiced by people with stroke and health professionals working in stroke rehabilitation. People with stroke and health professionals are willing to utilise HIIT interventions, however safety must be reassured through additional patient and clinician education and the provision of detailed guidance to support the use of HIIT in clinical practice. Some of the identified barriers and facilitators were specifically related to HIIT, although many were consistent with those identified in relation to exercise after stroke (Moncion et al., 2020; Simpson et al., 2011).

It appears from this study's findings that people with stroke and health professionals are keen to engage in HIIT, even though HIIT is rarely undertaken. This is positive for the implementation of HIIT. People with stroke who have engaged with HIIT largely enjoy the intervention and identified benefits in physical function and daily life which outweighed the hard work required from the intervention (Signal et al., 2016). Health professionals also appear to be happy to include high intensity interventions within clinical practice, however uncertainty about how to achieve this is evident. Self-efficacy in delivering high intensity interventions may be increased with appropriate screening and monitoring of participants prior to, and during the intervention, respectively (Connell et al., 2018).

Understanding and managing the barriers and facilitators specific to HIIT will be important to improve implementation. One simple strategy to start with might in the changing the terminology used by health professionals or even avoiding the phrase 'high intensity' when discussing HIIT. This is a novel finding from this study. The focus rather should be placed on the interval components of the intervention, rather than the intensity of the 'on' periods. Current exercise guidelines for people with stroke highlight the need for person-centred education and appropriate monitoring before and during exercise (Billinger et al., 2014). However, further recommendations are needed to account for the demands of HIIT after stroke.

To the best knowledge of the candidate this is the first study to explore perceptions of HIIT amongst people with stroke and health professionals working in stroke rehabilitation. As reported by people with stroke and health professionals in this study, concerns about safety during a HIIT intervention was reported as a barrier to engagement. While safety concerns are not commonly reported as a barrier to engagement in general aerobic exercise after stroke (Prout et al., 2017), people with stroke may be concerned about safety with HIIT due to the higher intensity of exercise prescribed. People with stroke within this study raised concerns regarding high blood pressure, falling, and increased anxiety with the high intensity aspect of the HIIT intervention. To date, no adverse events have been reported following the use of a HIIT intervention within the post-stroke population (Boyne et al., 2023; Crozier et al., 2018; Gjellesvik et al., 2021). To be included in these studies, participants were required to be a minimum of three months post-stroke (Boyne et al., 2016; Boyne et al., 2023), able to walk independently (Boyne et al., 2016; Boyne et al., 2023; Crozier et al., 2018; Gjellesvik et al., 2021), and were not diagnosed with an unstable cardiac condition (Boyne et al., 2016; Boyne et al., 2023). Therefore, pre-intervention screening may have attributed to the lack of adverse events reported.

While concerns regarding blood pressure appear to be common within the literature, this is not supported as a barrier to HIIT prescription. Indeed, protocols are recommended to gradually increase exercise intensity over a 10-second period at the commencement of the 'on' period to reduce the risk of hypertensive events (Lucas et al., 2015). Interestingly, a fear of falling was reported as a significant barrier to participation in general exercise by people with stroke in a quantitative study conducted by Gagnon and colleagues (2022) in Quebec. Despite the increased intensity of exercise required in HIIT, and potential fatigue (Valkenborghs et al., 2019), people with stroke in the current study did not report a fear of falling as a barrier to participation.

It should be noted that barriers to participation in exercise after stroke may vary depending on the personal and cultural characteristics of the person with stroke. For example, the severity of post-stroke impairments and subsequent reliance on others for assistance may pose a barrier to participation in exercise after stroke (Reicherzer et al., 2022). Additionally, low health literacy or the protection of family and friends may hinder participation to

exercise as illustrated in a study conducted in Benin, a small country in Africa (Noukpo et al., 2023). These barriers were not reported in the current study which may be associated with a potential lack of diversity obtained within this study.

Health professionals identified a lack of knowledge and/or confidence in prescribing HIIT and being able to adapt or individualise the intervention to the person with stroke's impairments in the current study. These barriers have previously been reported regarding the prescription of general exercise after stroke (Condon & Guidon, 2018; Moncion et al., 2020). Continued professional development (Sadler et al., 2011) and refinement of safety criteria and assessment (Billinger et al., 2014) are considered potential methods to overcome this barrier to the prescription of exercise after stroke. Further research is needed to highlight the use and benefits of HIIT post-stroke, as well as the need for continued professional development courses to increase knowledge and self-efficacy of health professionals with the intervention (Connell et al., 2018). Professional development courses for the multidisciplinary team could include information regarding what is HIIT, possible modifications, safety precautions and potential benefits to allow for informed medical clearance and how adequate supervision can be provided. Furthermore, the involvement of lived experts, that is, health professionals delivering exercise interventions, in the development of high intensity exercise protocols has also been suggested as desirable (Connell et al., 2018). Therefore, implementation of HIIT protocols could involve consideration of local context as well as include details regarding screening and monitoring, and how a protocol can be amended depending upon client presentation and clinical context.

6.6.1 Limitations

There was limited diversity in both groups of participants recruited to this study. People with stroke were mostly in the chronic stage of recovery, were independently mobile and most reported a strong exercise history before their stroke, with many considering themselves active post-stroke. In addition, 50% of respondents reported previous participation in HIIT which may not be representative of the participation rates in the wider stroke community. It is possible that the people with stroke who were earlier in their recovery period or had more mobility impairments may have expressed different

perceptions of HIIT. Similarly, there was also limited diversity within the health professional population, with majority of participants identifying as exercise physiologists or physiotherapists. While the provision of exercise is the primary practice for these professionals (Australian Physiotherapy Association, 2011; Exercise and Sport Science Australia, 2015), the inclusion of other members of the multidisciplinary team (e.g., medical practitioners, clinical nurse specialists) may have provided different perspectives. Approximately three-quarters of the health professionals who completed the questionnaire, reported having previously prescribed HIIT to people with stroke. It is unclear whether this is representative of the wider population of allied health clinicians. Therefore, findings from this study may not be generalisable to most stroke rehabilitation facilities.

Approximately one-third of participants who completed the questionnaire agreed to complete the interview. Although the sample recruited achieved data saturation (Hennink et al., 2017) it is possible that with numerous participants not completing all stages of this study (i.e., screening, questionnaire, and interview) that there is a risk of sampling bias (Dillman et al., 2014). An online platform (i.e., REDCap) was used to increase the accessibility and ease of completion questionnaire; however, evidence suggests response rates are lower compared to paper-based methods (Petchenik & Watermolen, 2011). However, the questions were co-designed with consumers to ensure areas of interest were targeted in an appropriate manner.

6.6.2 Future directions

To optimise the clinical implications of research results, future studies must expand the sample size and diversity of participants to allow for greater generalisability of results. At present, this data is limited to an Australian cohort, therefore it could be argued that an international perspective may broaden the findings. The use of focus groups during a professional setting (e.g., professional development event or conference workshop) may be utilised to increase the volume of health professional qualitative data collected. Therefore, further studies should aim to include a more diverse cohort of people with stroke and health professions, including Aboriginal and/or Torres Strait Islander peoples, people from culturally and linguistically diverse backgrounds, and various professions, respectively.

6.7 Conclusion

The findings of this mixed methods study suggest that people with stroke and health professionals who work with people with stroke believe HIIT to be beneficial. However, additional education on HIIT, safety procedures, and its benefits after stroke are needed to optimise participation and prescription. While HIIT is not included in the National Stroke Foundation recommendations, HIIT shows promise as an intervention to improve functional outcomes and is of interest to people with stroke. High quality randomised controlled trials and systematic reviews are needed to identify the effectiveness of HIIT post-stroke to allow for integration into the National Stroke Foundation guidelines.

6.8 Implementation of this evidence in this program of research

While this exploratory cross-sectional mixed methods study contains a small sample size, this study found people with stroke and health professionals who work with people with stroke consider HIIT to be a suitable intervention. However, action must be taken to increase the willingness of people with stroke to participate, and the confidence of health professionals to prescribe such a program. Similar barriers and facilitators to HIIT are reported for general exercise and physical activity (Gaskins et al., 2021; Moncion et al., 2020; Nicholson et al., 2017; Simpson et al., 2011), therefore steps must be taken to overcome these barriers to increase the uptake of HIIT in stroke rehabilitation. Within this program of research, HIIT is to be provided in the RCT protocol described in Chapter 9. The screening/consenting process and the participant information sheet will include extensive information regarding the HIIT protocol, actions to ensure safety and individualisation (i.e., according to participant impairment and goals) as well as the experience of the therapist providing the intervention (i.e., university qualification and experience in the provision of HIIT).

Chapter 7 STUDY 3: BIOMARKERS FOR OPTIMISING REHABILITATION AND INDIVIDUALISED INTERVENTIONS: BDNF VERSUS LACTATE

7.1 Preface

Biomarkers of neurological recovery, including BDNF, are considered useful indicators of the effectiveness of rehabilitation interventions (Cassidy & Cramer, 2017). High intensity aerobic exercise can elicit significant increases in BDNF as indicated by the systematic review and meta-analysis presented in Study 1, Chapter 5 of this thesis. BDNF concentration is commonly analysed using the ELISA protocol (Gonzalez et al., 2018), but this method requires specialised and costly equipment and training for blood collection and analysis, making it impractical for routine use in the clinical setting. An alternative biomarker associated with synaptic plasticity and high intensity exercise that can be measured in clinical practice may be more feasible than BDNF in stroke rehabilitation settings. Blood lactate is associated with BDNF secretion (El Hayek et al., 2019) and high intensity aerobic exercise and neural function (Skriver et al., 2014). The measurement of lactate concentration using fingerprick blood sampling is within the scope of practice of health professionals, such as physiotherapists (Australian Physiotherapy Association, 2011) and exercise physiologists (Exercise and Sports Science Australia, 2015).

A pre-post study design was conducted to identify the relationship between BDNF and lactate concentration at rest and following a single bout of high intensity aerobic exercise in a group of healthy adults. This study was originally intended to explore the relationship between lactate and BDNF concentrations in a stroke cohort compared to a healthy control group. The aim was to identify any discrepancies in the relationship between BDNF and lactate attributed to the effect of the stroke. However, the Covid-19 public lockdowns in metropolitan Sydney from June to October 2021 led to the restriction of some research to reduce risk of infection in vulnerable populations. As a result, this study solely focuses on a healthy adult cohort.

7.2 Abstract

Objective. To identify the relationship between BDNF and blood lactate concentrations before and after a submaximal exercise test.

Methods*.* Healthy adults were recruited to complete a submaximal cycle ergometer exercise test. Brain-Derived Neurotrophic Factor (BDNF) and blood lactate concentrations were measured before and after a submaximal graded exercise test. BDNF concentration was measured using the Enzyme-Linked Immunosorbent Assay method and lactate was measured using the Lactate Pro 2 Analyser. Pearson correlation coefficient was used to examine the relationship between BDNF and lactate concentration at pre-exercise, post-exercise, and the change in concentrations (post- minus pre-intervention).

Results. Thirty-one healthy adults (mean ± SD 37.5 ± 14.0 years, 17 (54.8%) female) participated in this study. BDNF concentration was 15.46 ± 3.89 ng/mL at pre-exercise and 17.74 ± 3.92 ng/mL post-exercise. Lactate concentration was 2.52 ± 0.92 mmol/L at pre-exercise and 11.17 ± 3.34 mmol/L post-exercise. Poor correlation was observed between BDNF and lactate concentration at pre-exercise ($r = -0.256$, $p = 0.164$) and post-exercise ($r = 0.112$, $p = 0.549$). A poor correlation was observed in the change in BDNF and lactate concentrations from pre- to post-exercise ($r = 0.019$, $p = 0.921$).

Conclusions. BDNF and lactate are poorly correlated at pre- and post-exercise. While both BDNF and lactate show concomitant increases following an acute bout of exercise, there is little evidence to suggest a relationship between the two blood biomarkers.

7.3 Introduction

Brain-Derived Neurotrophic Factor (BDNF) is essential for brain development and neuronal survival within the central and peripheral nervous systems (Molinari et al., 2020). Higher levels of basal BDNF are associated with cognitive processes such as memory formation and recall (van Dongen et al., 2016; Zenke et al., 2015) and brain repair following injury (Liu et al., 2020). Neurological conditions, such as stroke (Pedard et al., 2018; Wlodarczyk et al., 2021) and the presence of the Val66Met polymorphism (Egan et al., 2003; Hariri et al., 2003) are associated with reductions in basal BDNF concentrations. The Val66Met polymorphism is present in 20 to 30% of the White population and up to 70% within the Asian population (Knaepen et al., 2010). The Val66Met polymorphism is associated with reduced BDNF secretion (Egan et al., 2003; Hariri et al., 2003) and reduced concentration increase

following exercise (Lemos et al., 2016). Lower BDNF concentration is associated with poorer outcomes following neurological events like stroke (Liu et al., 2020; Pikula et al., 2013; Wang et al., 2017; Weinstein et al., 2014).

As demonstrated in the systematic review and meta-analysis presented in Study 1 (Chapter 5), exercise increases BDNF concentration. High intensity aerobic exercise can produce large and statistically significant increases in BDNF concentration following stroke (Hsu et al., 2021), and might attenuate the age- (Walsh et al., 2020) and injury-related BDNF reduction observed after stroke (Mackay et al., 2017). Higher BDNF concentrations can facilitate improvements in cognitive function (Weinstein et al., 2014) and functional recovery following neural injury, such as stroke (Liu et al., 2020; Wang et al., 2017). BDNF is a biomarker of neuroplasticity (Balkaya & Cho, 2019; Bang, 2017) and may provide an indirect assessment of the effectiveness of rehabilitation during stroke recovery (Liu et al., 2020). BDNF testing typically involves specialised phlebotomy and biochemistry training, and expensive equipment (Gonzalez et al., 2018). The allied health professionals working with people with stroke in rehabilitation typically won't have the necessary training or equipment to administer the BDNF blood draw and analysis. While BDNF analysis can be outsourced, this is often an expensive and logistical challenge (Gonzalez et al., 2018).

Lactate is another biomarker that is also responsive to exercise with increases in concentration observed following high intensity aerobic exercise (Tsukamoto et al., 2015). Lactate concentration is easier to measure in clinical practice, requiring a smaller blood sample (0.3μL versus 8mL for BDNF concentration analysis), and no specialised training or equipment (Bonaventura et al., 2015; Crotty et al., 2021). While lactate concentration is commonly used as a measure of exercise intensity (Skriver et al., 2014; Tsukamoto et al., 2015; Tsukamoto et al., 2016), a correlation may exist between BDNF and lactate concentration (Antunes et al., 2020; Ferris et al., 2007; García-Suárez et al., 2020; Rojas Vega et al., 2006). However, no clear relationship between BDNF and lactate concentrations are demonstrated in post-stroke literature. Therefore, the original aim of this study was to identify the relationship between BDNF and blood lactate concentrations before and after a submaximal exercise test in a stroke cohort, compared to a healthy control cohort.

As a result of the Covid-19 lockdowns experienced in Sydney from 27th June 2021 to 11th October 2021 and changes in personnel at the recruitment hospital halting patient screening, this study had to be amended. While initially this study was intended to be completed with participants with and without stroke, the current study was completed in a solely healthy population. Access to ACU staff and students, as well as professional networks of the research team, facilitated the recruitment of a healthy cohort. While the relationship between BDNF and lactate concentration has been explored in healthy young adults (Antunes et al., 2020; Ferris et al., 2007), there is very little understanding about the relationship in older adults and women of any age. Therefore, the aim of this current study is to identify the relationship between BDNF and lactate concentrations before and after a submaximal graded exercise test in a healthy cohort. It was hypothesised BDNF genotype and biological sex would impact the relationship between BDNF and lactate concentration.

7.4 Methods

A pre-post observation study design was used to explore the change in BDNF and lactate concentration and the correlation between these biomarkers before and after a submaximal graded exercise test in a healthy adult population. Ethics approval was obtained from Royal Prince Alfred Hospital HREC (X21-0432), Royal Rehab Research Governance Office (2021-ETH12179), and ACU HREC (2022-2698RC).

7.4.1 Participants

To be powered to detect change in BDNF concentration, a minimum of 24 participants were required to be recruited for this study. Healthy adults were recruited for this study. Participants were recruited via social media (e.g., Facebook, LinkedIn, Twitter/X) and via the personal and professional networks of the research team. Adults needed be cleared to exercise using the ESSA Adult Pre-Exercise Screening System tool (APSS, version 2, ESSA, 2019). This screening tool comprised the collection of demographic data (i.e., age, sex, BMI) and current exercise levels reported as weighted exercise per week (total minutes = (minutes of light exercise) + (minutes of moderate exercise) + (2 x minutes of vigorous/high exercise). A detailed explanation of the inclusion criteria and the recruitment method for this study are outlined in Chapter 4.2 Participants and Chapter 4.4 Recruitment.

7.4.2 Procedure

All participants were required to complete a submaximal graded exercise test, with blood collected immediately before and after. A more detailed explanation of the procedure of this study is presented in Chapter 4.7.1 Procedure.

7.4.2.1 Submaximal graded exercise test

All participants completed a submaximal graded exercise test on an upright cycle ergometer (Monark Ergomedic 828E). A stroke protocol (Yates et al., 2004) was used to allow comparison between the stroke and healthy cohorts. For healthy participants, the stroke protocol was modified to account for the increased fitness of a healthy cohort compared to the stroke population. Participants were required to cycle at 50-70 RPM, with the resistance and/or cadence increased every three-minutes until 90% of age-predicted heart rate maximum was achieved. The test was ceased if the participant reported near-maximal effort (i.e., 18/20 RPE), angina and/or dyspnoea (Wilson & Jones, 1989). The participant was encouraged to complete a cool-down (i.e., cycling with zero resistance at a slow cadence) after the blood collection post-exercise if desired.

7.4.2.2 Blood collection

Blood was collected immediately before and after the submaximal graded exercise test to identify changes in BDNF and lactate concentration. Pre-exercise blood samples were collected after the participant laid still on a plinth for approximately 10-minutes. Significant reductions in BDNF concentration are observed after 10 to 15-minutes of rest following the cessation of a ramp protocol (Rojas Vega et al., 2006), therefore venous and fingerprick blood samples were collected within five-minutes of test completion in this study. Two venous and fingerprick blood samples were collected before exercise, and one sample of each were collected after exercise.

7.4.3 Outcome measures

The primary outcome for this study is the relationship between BDNF and lactate concentrations at pre-exercise, post-exercise, and change (i.e., post- minus pre-exercise). BDNF concentration was analysed from venous serum samples collected using the ELISA method (ab212166, Abcam, Cambridge, MA), reported as ng/mL. BDNF genotype (i.e.,

presence or absence of the Val66Met polymorphism) was detected by TaqMan genotyping probe assay using the QuantStudio™ 3 System. Samples with the wild type nucleotide G in position 196 (c.196G) were reported as “without the Val66Met polymorphism. Samples that were heterozygous c.196G>A or homozygous c.196G>A were reported as “with the Val66Met polymorphism”. Lactate concentration was analysed from fingerprick blood samples, reported as mmol/L. Additional detail is provided in Chapter 4.7.1 Procedure.

7.4.4 Data analysis

Data were entered into REDCap by the research team, downloaded and imported into SPSS for analysis (IBM SPSS Statistics, version 29.0.1.0). Demographic data of the participants are presented as mean, standard deviation, and percentages where appropriate. Change in concentration was calculated by subtracting the pre-exercise concentration from the post-exercise concentration. Two-Sided Paired Sample T-Tests were used to determine the significance of the change in BDNF and lactate concentrations. Subgroup analyses were conducted to explore the effect of BDNF genotype and sex on the concentration and correlation of BDNF and lactate.

Histograms were used to visually observe the normality of the outcome measures (BDNF and lactate concentrations at pre-exercise, post-exercise, and change) which demonstrated a normal distribution. Scatterplots were used to visually examine the nature of the relationships between the BDNF and lactate concentrations. Pearson correlation (r) was used to examine the relationship between BDNF and lactate concentrations at pre-exercise, post-exercise and between the change scores of both biomarkers (Akoglu, 2018). A perfect correlation was taken at +/- 1, a very strong correlation between +/- 0.8 and +/- 0.9, a moderate correlation between +/- 0.6 and +/- 0.7, a fair correlation between +/- 0.3 to +/- 0.5, and a poor correlation between +/- 0.1 and +/- 0.2 (Akoglu, 2018). Significance was set at $p < 0.05$. A one-way ANOVA was conducted to explore whether fitness level had an impact on change in BDNF and lactate concentration (i.e., after minus before).

7.5 Results

7.5.1 Participants

Thirty-one healthy adults (17 females, 54.8%) aged 37.5 ± 14.0 (range; 20 – 70) years were recruited to this study. The characteristics of the participants are presented in Table 7-1.

Table 7-1 Participant characteristics

Characteristics	**Participants**
Age (years)	37.52 ± 14.02
Sex (F)	17 (54.8)
BMI (kg/m^2)	24.33 ± 3.27
VO_{2peak} ($mL.kg.m^2$)	43.0 ± 10.90
Weighted exercise per week (min/week) (ESSA APSS, version 2, 2019)	415 ± 450 (range; 50-2,520)
Val66Met polymorphism	11 (35)
Self-reported ethnicity	
White	27 (87)
Asian	1 (3)
Other (e.g., Greek, Italian)	3 (10)

Note: Values are mean ± standard deviation or frequency (percentage). Weighted exercise = (minutes of light exercise + minutes of moderate exercise) + (2 x minutes of vigorous/high exercise).

Abbreviations – F: Female, BMI: Body mass index, ESSA APSS: ESSA Adult Pre-Exercise Screening System, Val66Met: Substitution of a valine (Val) with a methionine (Met) at codon 66 of the BDNF gene.

7.5.2 Neuroplasticity biomarker concentrations

Table 7-2 and Table 7-3 present the BDNF and lactate concentrations before and after the submaximal graded exercise test. A statistically significant increase in BDNF and lactate concentrations were observed when analysing the change from pre-exercise to post-exercise ($p < 0.001$). In the sample of 31 participants, BDNF concentration was 15.46 ± 3.89 ng/mL at pre-exercise and 17.74 ± 3.92 ng/mL post-exercise. Lactate concentration was 2.52 ± 0.92 mmol/L at pre-exercise and 11.17 ± 3.34 mmol/L post-exercise.

Table 7-2 BDNF (ng/mL) before and after the submaximal graded exercise test

	Pre-exercise (mean ± SD)	Post-exercise (mean ± SD)	Change (post-exercise minus pre-exercise) (mean (95% CI))
Full sample (n = 31)	15.46 ± 3.89	17.74 ± 3.92	1.95 (1.21 – 3.35)**
Female (n = 17)	16.08 ± 4.19	17.28 ± 4.23	1.21 (-0.47 – 2.88)
Male (n = 14)	14.71 ± 3.49	18.30 ± 3.59	3.59 (2.55 – 4.63)**
Without Val66Met (n = 20)	15.75 ± 4.13	17.97 ± 4.23	2.22 (0.74 – 3.70)*
With Val66Met (n = 11)	14.94 ± 3.52	17.33 ± 3.44	2.39 (0.67 – 4.11)***

* p = 0.005 ** p < 0.001 *** p = 0.011

Abbreviations – BDNF: Brain-Derived Neurotrophic Factor, SD: Standard deviation, CI: Confidence interval, mg/mL: Milligrams per millilitre.

Table 7-3 Lactate (mmol/L) before and after the submaximal graded exercise test

	Pre-exercise (mean ± SD)	Post-exercise (mean ± SD)	Change (post-exercise minus pre-exercise) (mean (95% CI))
Full sample (n = 31)	2.52 ± 0.92	11.17 ± 3.34	8.7 (7.42 – 9.90) **
Female (n = 17)	2.29 ± 1.01	11.33 ± 3.19	9.04 (7.47 – 10.60)**
Male (n = 14)	2.79 ± 0.76	10.99 ± 3.64	8.20 (5.99 – 10.41)**
Without Val66Met (n = 20)	2.55 ± 1.04	10.86 ± 3.07	8.31 (6.90 – 9.71)**
With Val66Met (n = 11)	2.46 ± 0.71	11.76 ± 3.88	9.30 (6.56 – 12.04)**

* p = 0.005 ** p < 0.001

Abbreviations – BDNF: Brain-Derived Neurotrophic Factor, SD: Standard deviation, CI: Confidence interval, mmol/L: Millimoles per litre.

A one-way ANOVA found no significant effect of fitness level on change in BDNF concentration ($F(1,29) = .343$, $p = .564$) nor change in lactate concentration ($F(1,29) = 2.984$, $p = .095$) following exercise.

7.5.3 Correlation between neuroplasticity biomarkers

Table 7-4 presents the correlation between BDNF and lactate concentrations before and after the submaximal graded exercise test. Figures 7-1, 7-2, and 7-3 display the scatterplot of the relationship between BDNF and lactate concentration at pre-exercise, post-exercise, and the change score, respectively. A poor, not statistically significant correlation was observed at pre-exercise, post-exercise and when examining the change scores of both biomarkers in the whole sample.

Table 7-4 Correlation between BDNF and lactate concentrations

	Whole sample (n = 31)
Pre-exercise correlation	r = -0.256, (p = 0.164)
Post-exercise correlation	r = 0.112 (p = 0.549)
Change (post-exercise minus pre-exercise) correlation	r = 0.019 (p = 0.921)

Abbreviations – r: Pearson correlation.

* Significant correlation.

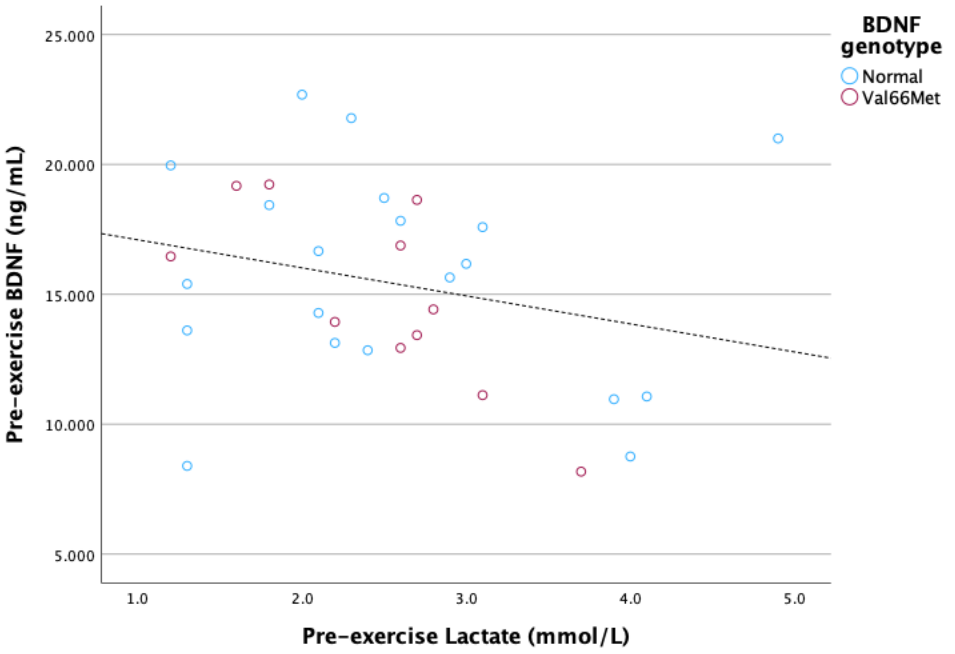


Figure 7-1 Scatterplot of relationship between BDNF and lactate at pre-exercise

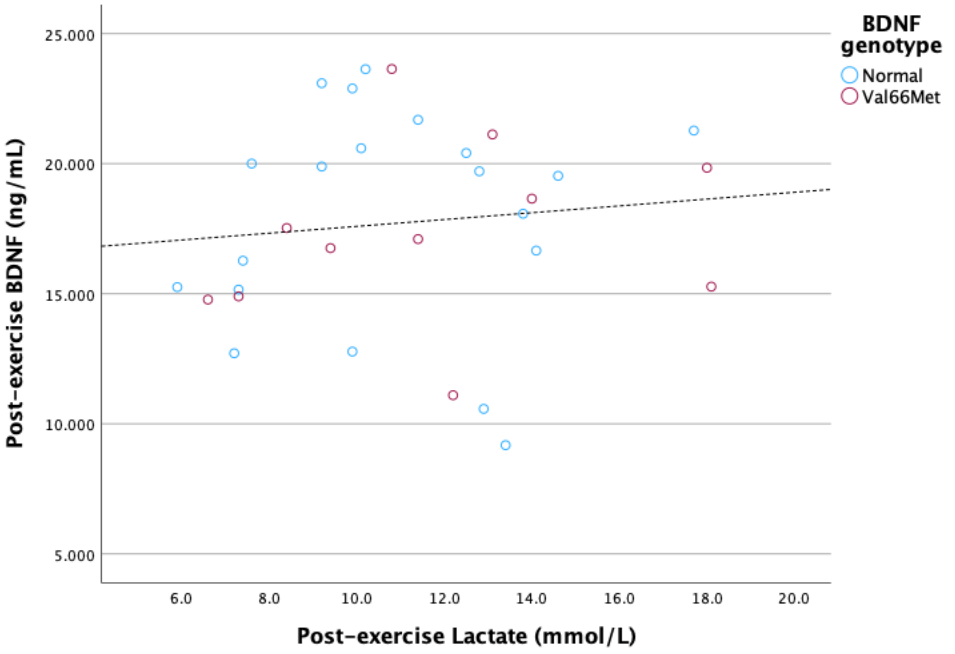


Figure 7-2 Scatterplot of relationship between BDNF and lactate at post-exercise

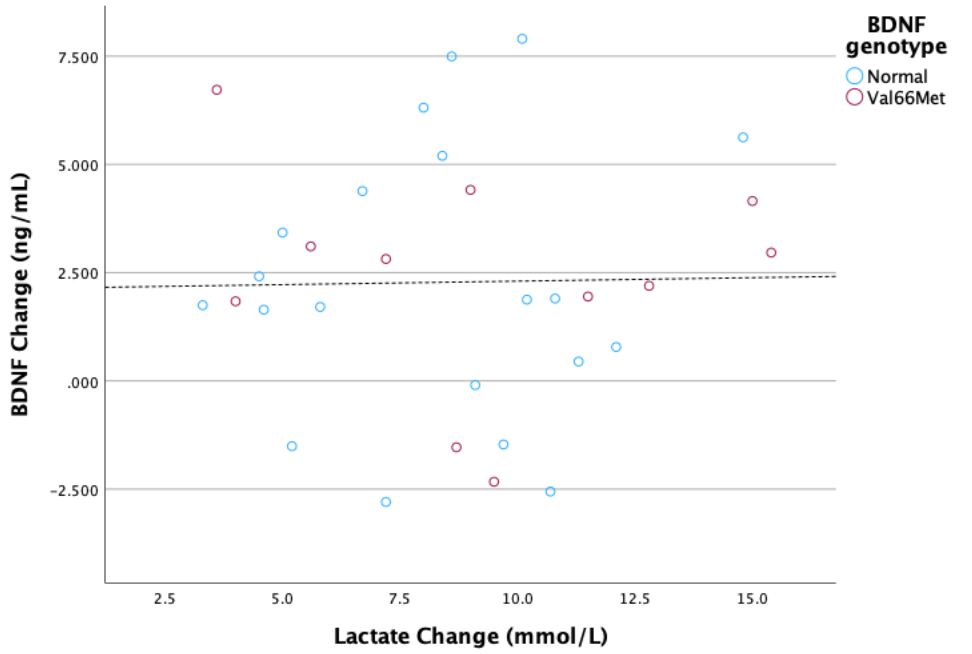


Figure 7-3 Scatterplot of relationship between BDNF and lactate change (post-exercise minus pre-exercise)

7.5.4 Subgroup analyses

Subgroup analyses were conducted to explore the correlation between BDNF and lactate concentration accounting for two potential confounders of BDNF concentration (i.e., presence of the Val66Met polymorphism and biological sex).

Effect of the presence of the Val66Met polymorphism

When observing the change in BDNF concentration, a statistically significant increase was observed in participants without ($p = 0.005$) and with ($p = 0.011$) the Val66Met polymorphism. A statistically significant change in lactate concentration was observed in participants without and with the Val66Met polymorphism ($p < 0.001$). There was no statistically significant difference in the BDNF concentration at pre-exercise ($p = 0.574$), post-exercise ($p = 0.656$) or when observing the change following the submaximal graded exercise test ($p = 0.873$) when comparing participants without and with the Val66Met polymorphism. No statistically significant difference was observed in lactate concentration between participants with and without the Val66Met polymorphism at pre-exercise ($p = 0.956$), post-exercise ($p = 0.664$), and change in concentration ($p = 0.667$).

When accounting for the presence of the Val66Met polymorphism, a moderate, statistically significant inverse correlation was observed between BDNF and lactate concentrations at pre-exercise ($r = -0.744$, $p = 0.009$). A poor correlation was observed at post-exercise ($r = 0.200$, $p = 0.555$), and when comparing the change between both biomarkers in participants with the Val66Met polymorphism ($r = -0.121$, $p = 0.722$). No statistically significant correlation was observed at pre-exercise ($r = -0.117$, $p = 0.624$), post-exercise ($r = 0.086$, $p = 0.718$) or when comparing the change in BDNF and lactate in participants without the Val66Met polymorphism ($r = 0.094$, $p = 0.693$).

Effect of biological sex

When observing the change in concentration in females, a not statistically significant increase in BDNF ($p = 0.147$) and a statistically significant increase in lactate ($p < 0.001$) was identified. A statistically significant increase in BDNF and lactate concentration was observed in male participants following the submaximal graded exercise test ($p < 0.001$). There was no statistically significant difference in the BDNF concentration at pre-exercise ($p = 0.481$), and post-exercise ($p = 0.232$) between female and male participants. There was a statistically significant difference between female and male participants when observing the change in BDNF concentration following the submaximal graded exercise test ($p = 0.021$). No statistically significant difference was observed in lactate concentration between male and female participants at pre-exercise ($p = 0.300$), post-exercise ($p = 0.899$), and change in concentration ($p = 0.690$).

When the relationship between BDNF and lactate concentrations was examined in females, no correlation was observed at pre-exercise ($r = 0.023$, $p = 0.931$), post-exercise ($r = 0.053$, $p = 0.840$) or when comparing the change in concentration ($r = 0.084$, $p = 0.748$). When the relationship between BDNF and lactate concentrations were examined in males, a moderate, statistically significant inverse correlation was observed between the BDNF and lactate concentrations at pre-exercise ($r = -0.695$, $p = 0.006$). No correlation was observed between the two biomarkers at post-exercise ($r = 0.207$, $p = 0.477$) or when comparing the change in concentration between BDNF and lactate in the male participants ($r = 0.083$, $p = 0.779$).

7.6 Discussion

This pre-post intervention study demonstrates no correlation between BDNF and lactate concentration before, after or when comparing change following a submaximal graded exercise test. Subgroup analyses identified a moderate inverse correlation between BDNF and lactate concentration before exercise in participants with the Val66Met polymorphism, but no correlation at post-exercise or in concentration change, or at any timepoint in participants without the Val66Met polymorphism. No correlation was identified at any timepoint in female participants. A statistically significant inverse correlation was identified between BDNF and lactate concentration at pre-exercise in male participants, but no correlation was found at post-exercise or in concentration change.

This current study identified no correlation between BDNF and lactate concentration following the exercise test. These results do not align with existing literature. Previous research has identified an inverse relationship when comparing BDNF and lactate concentrations change following a session of HIIT (Antunes et al., 2020) and graded exercise test (Ferris et al., 2007). Characteristics of the sample may account for these differences. This current study comprised more female than male participants, and participants were older compared to previous studies (Antunes et al., 2020; Ferris et al., 2007). It has been proposed that hormonal changes associated with the menstrual cycle may alter BDNF concentration (Begliuomini et al., 2007). Furthermore, serum BDNF concentration reduces with increased age (Erickson et al., 2010; Lommatzsch et al., 2005; Ziegenhorn et al., 2007), however the effect of increased age on lactate concentration is an area for further research (Brooks et al., 2022). Therefore, the inclusion of female and older participants may have impacted the BDNF concentration, and therefore the correlation between BDNF and lactate.

No previous study has accounted for the presence of the Val66Met polymorphism, which may account for the lack of a relationship between the biomarkers found in the current study. The Val66Met polymorphism is attributed to reduced BDNF production and secretion at rest (Knaepen et al., 2010). In response to exercise, the presence of the Val66Met polymorphism is linked to stunted BDNF secretion, with a higher intensity of exercise required to facilitate the same increase as an individual without the polymorphism (Mang et al., 2013). One study identified no effect of the Val66Met polymorphism on memory recall

following exercise in a sample of 36 undergraduate students (Ballester-Ferrer et al., 2022). While BDNF concentration was not measured, a positive correlation between lactate at 15-minutes post-exercise and memory recall at 48-hours was reported ($r = 0.363$, $p = 0.002$) (Ballester-Ferrer et al., 2022) which may be linked with BDNF concentration. However, the results of the current study are more consistent with the growing body evidence suggesting the Val66Met polymorphism does not have significant effects on BDNF concentration in healthy adults (Helm et al 2017, Kambestad et al 2023).

Interestingly, the amount of change observed following the submaximal exercise test, was higher for lactate concentration than BDNF. Differences in lactate and BNDF responses to exercise may account for this. The concentration of blood lactate during exercise is dependent upon the rate of secretion and uptake within the body (Gladden, 2004; van Hall, 2010). Lactate accumulation within the blood begins to increase upon the start of moderate intensity exercise, decreasing after some time with the rate of decrease dependent upon exercise intensity (van Hall, 2010). Prolonged exposure to high intensity exercise produces large increases in lactate concentration (Garcia-Suarez et al., 2010), such as an acute session of HIIT. In addition, the recruitment of fast twitch muscle fibres elicited during high intensity exercise are more suited to lactate production compared to slow twitch fibres (Gladden, 2004). While BDNF is also secreted within skeletal muscle (Yilmazer et al., 2019), it is believed that the muscle damage associated with exercise may be necessary to induce BDNF expression (Renteria et al., 2022). However, muscle-derived BDNF may not enter the bloodstream in response to exercise as demonstrated in pre-clinical models (Matthews et al., 2009). Therefore, it may be possible that participants who exercised at higher workloads for longer during the submaximal graded exercise test undertaken in this current study may record larger changes in lactate concentration, but not BDNF.

7.6.1 Limitations

Although this study originally planned to include a healthy cohort, the effects of the Covid-19 pandemic on recruitment did not allow people with stroke to be included in this study. Several potential participants chose not to participate in this study because numerous blood draws were required. Limited heterogeneity was evident within the participant cohort included in this study. Study participants were close in age, had a strong exercise history,

and less than half possessed the Val66Met polymorphism which may limit generalisability to the wider adult population. Although subgroup analyses were conducted as a preliminary investigation of confounders to BDNF concentration, the study was not powered for such, and future studies should explore potential BDNF confounders including physical fitness or menstrual cycle phase. In addition, the narrower range of the increases in BDNF concentration compared to those of lactate may limit the capacity to find substantial correlations between these two measures. Individuals with a higher lactate threshold because of endurance training (Razanskas et al., 2015) or increased lactate transport because of involvement in HIIT (Siahkouhian, Khodadadi, Shahmoradi, 2013) may have impacted the lactate results collected in this study. Numerous participants within this study were highly trained (e.g., Olympic athlete, endurance athlete) who undertake regular endurance or high intensity training. It should also be noted that a correlation between BDNF and lactate concentration does not equal agreement between the two measures, therefore lactate should not be used as an alternative to BDNF without further investigation.

7.6.2 Future directions

To optimise the implications of this research, the inclusion of a larger, more diverse sample is warranted to detect the relationship between BDNF, and lactate concentration and allow for the analysis of potential confounders of BDNF and lactate. These confounders may include age, ethnicity, physical fitness, and BMI. The initial aim of this study was to examine the relationship between BDNF and lactate concentrations in people with stroke before and after a submaximal graded exercise test, and to compare the results with a healthy, age and sex-matched control group. A minimum sample size of 45 participants is required to detect change in BDNF concentration following a graded exercise test in people with stroke (Boyne et al., 2020), therefore this sample is recommended to allow a powered analysis of the relationship between BDNF and lactate concentrations in a stroke cohort. To allow for a strong subgroup analysis, a larger sample size is recommended. Due to the host of benefits for people with stroke elicited by a HIIT, future studies should identify the relationship between BDNF and lactate concentrations before and after a single HIIT session.

7.7 Conclusion

Overall, the findings of this pre-post observational study suggest that BDNF and lactate concentrations are not correlated at pre-exercise, post-exercise or when comparing change in concentration in a mixed sex adult cohort. Subgroup analyses identified a moderate inverse correlation between BDNF and lactate concentration pre- exercise in participants with the Val66Met polymorphism and in male participants, only. While BDNF and lactate concentrations are responsive to increasing exercise intensity in a healthy population, lactate may not be a suitable alternative to the measurement BDNF concentration as a biomarker of neuroplasticity.

7.8 Implementation of this evidence in this program of research

To further explore the relationship between BDNF and lactate correlation in response to acute and chronic exercise, the measurement of BDNF and lactate concentrations are included in the randomised controlled trial protocol (Study 5, Chapter 9). At present, no studies have explored the direct relationship between BDNF and lactate concentration after stroke, although, one study has demonstrated no change in BDNF concentration despite significant increases in lactate concentration following acute exercise (Charalambous, Helm, et al., 2018). Therefore, the relationship between BDNF and lactate concentration should be explored in people with stroke to assist the use of biomarkers of neuroplasticity in clinical practice.

Chapter 8 STUDY 4: RELATIONSHIP BETWEEN THE MOTOR ACTIVITY LOG AND THE RATING OF EVERYDAY ARM-USE IN THE COMMUNITY AND HOME IN AN AUSTRALIAN POST-STROKE POPULATION

8.1 Preface

One of the main goals of CIMT and mCIMT is the translation of increased paretic limb use to daily life (Taub et al., 2006; Taub et al., 2013), promoting increased QoL (Kwakkel et al., 2015) and functional independence (Abdullahi et al., 2020). The MAL-30 (i.e., MALAOU, MALQOM) (Uswatte et al., 2006) and REACH (Simpson et al., 2013) are assessment tools used to quantify paretic arm use in the community and at home. The MALAOU provides information on the amount of use of the paretic limb, while the MALQOM provides information on quality of paretic limb use, however neither elaborate on how this limb is used (e.g., comparison to non-paretic limb or pre-stroke use) (Simpson et al., 2013). In addition, the MALAOU and MALQOM rely on subjective participant ratings of the quality of upper limb use (van der Lee et al., 2004), while the REACH utilises clear descriptions and an algorithm to quantify use (Simpson et al., 2013). The MALAOU and MALQOM are commonly used to assess the effectiveness of CIMT and mCIMT interventions (Abdullahi, 2018), however emerging evidence in a Canadian cohort suggests the REACH is strongly correlated with the MALAOU 14-item scale (Simpson et al., 2013).

A cross-sectional study design was implemented to identify the relationship between the MALAOU-30 and REACH, and the MALQOM-30 and REACH at baseline, and after an intensive upper limb rehabilitation intervention. Due to the impact of Covid-19, and subsequent difficulties with the recruitment of people with stroke in Sydney NSW, the ACU CIMT clinic within the Banyo Health Clinic in Brisbane was included as a recruitment site.

8.2 Abstract

Objective. To identify the relationship between the MALAOU-30, MALQOM-30 and the REACH at baseline, and after an intensive upper limb therapy program.

Methods*.* People with stroke completed a two-week upper limb therapy program. The MALAOU, MALQOM and REACH were conducted at pre-intervention and post-intervention. Spearman rank correlation coefficient was used to examine the relationship between the MALAOU and REACH, and the MALQOM and REACH scores at pre-intervention, post-intervention, and the change score.

Results. Ten people with stroke (63.90 ± 13.89 years old, 13.80 ± 7.86 months post-stroke, five dominant limb affected) completed the upper limb therapy program. A non-statistically significant correlation between the MALAOU and REACH was observed at pre-intervention (rho = 0.482, p = 0.227) and post-intervention (rho = 0.294, p = 0.480). A statistically significant correlation between the MALQOM and REACH was observed at pre-intervention (rho = 0.717, p = 0.02), but not at post-intervention (rho = 0.566, p = 0.088). A non-statistically significant correlation was observed when comparing change scores of the MALAOU and REACH (rho = -0.140, p = 0.740) and the MALQOM and REACH (rho = 0.021, p = 0.955).

Conclusions. The MALAOU and REACH are not correlated at pre-intervention and post-intervention. The MALQOM and REACH demonstrate a moderate correlation at baseline, but no correlation at post-intervention. Change scores of both tools are not correlated to the change scores of the REACH. A larger sample size is needed to identify if the REACH can be used as an alternative to the MAL in clinical practice.

8.3 Introduction

Learned non-use, resulting from numerous unsuccessful attempts to use the paretic upper limb (Molle Da Costa et al., 2019) and positive reinforcement from compensatory strategies to facilitate movement (Bakhti et al., 2017; Molle Da Costa et al., 2019) following stroke is common. Reductions in QoL and functional independence are evident with learned non-use (Kelly et al., 2018; Taub et al., 2006), therefore targeted rehabilitation implementing forced use of the paretic limb such as mCIMT is needed to facilitate increased real-world use (Miltner et al., 2016). Assessment tools such as the MAL (Uswatte et al., 2006) and REACH

(Simpson et al., 2013) were developed to quantify paretic upper limb use outside of the clinical setting.

The MAL-30 consists of two 30-item scales to identify the amount of paretic limb use (MALAOU) and the quality of paretic limb use (MALQOM) across an array of ADLs such as brushing teeth and turning a doorknob (Taub et al., 2011; Uswatte et al., 2006). The MAL was demonstrated to be an independent predictor of Action Research Arm Test score after stroke, indicating upper limb capacity (Chen et al., 2022). The MAL is considered useful for participants with some use of the paretic limb and adequate cognitive abilities to interpret the scale items and rate their use (Hammer & Lindmark, 2010). While the MALAOU and the MALQOM assess different parameters of paretic upper limb function (i.e., amount of use and quality of use, respectively), these two subscales are strongly correlated (Andrabi et al., 2022; van der Lee et al., 2004). Despite this, the MAL does not provide an indication into how participants are using the paretic limb during these tasks (e.g., only for stabilisation and not for manipulation of objects) (Simpson et al., 2013).

The REACH was developed by people with stroke, caregivers, and clinicians to provide meaningful information about the real-world use of the paretic upper limb (Simpson et al., 2013) including the impact on activity and participation (Obembe, Simpson & Eng, 2023). The REACH consists of two separate classification scales, depending on dominance of the paretic upper limb (i.e., if the paretic limb is the dominant or non-dominant limb) (Simpson et al., 2013). The REACH is also considered strongly related to the Action Research Arm Test (Simpson et al., 2013). The REACH is much shorter than the MAL 30-item scale, taking minutes to complete and can be conducted remotely, if necessary (Simpson et al., 2013), and therefore may be more feasible in clinical practice due to potential time constraints.

A strong correlation was identified between the REACH and the MALAOU 14-item scale in a Canadian sample of 96 older adults with a mean time post-stroke of seven years (Simpson et al., 2013). However, this correlation has not been explored using the MALAOU or MALQOM 30-item scale, nor in an Australian context. The MAL-30 assesses a broader range of ADLs when compared to the MAL-14 (Taub et al., 2011) which may provide additional insight into the amount and quality of paretic limb use. Therefore, the aim of this study is to explore the

relationship between the 30-item MAL (i.e., MALAOU and MALQOM) and the REACH scale. Based on existing correlations between the MALAOU-14 and REACH (Simpson et al., 2013), it was hypothesised the MALAOU-30 would demonstrate a significant relationship with the REACH.

8.4 Methods

A pre-post observational study was used to explore the change in MALAOU, MALQOM and REACH and the relationship between the MAL-30 and REACH before and after a two-week intensive upper limb therapy program in a post-stroke population. Ethics approval was obtained from Royal Prince Alfred Hospital HREC (X21-0432), Royal Rehab Research Governance Office (2021-ETH12179) and ACU HREC (2022-2698RC).

8.4.1 Participants

People with upper limb hemiparesis following stroke were recruited for this study. Participants were recruited via Royal Rehab Private Petersham and self-referral of individuals to the CIMT clinic at the Banyo Health Clinic. People with stroke were required to possess ≥10 degrees of active movement in the paretic limb (McNulty et al., 2015). A detailed explanation of the inclusion criteria and the recruitment method for this study are outlined in Chapter 4.2 Participants and Chapter 4.4 Recruitment.

8.4.2 Procedure

All participants were required to complete a two-week intensive upper limb program, with the MALAOU, MALQOM and REACH assessed before and after. A more detailed explanation of the procedure of this study is presented in Chapter 4.8.1 Procedure.

All participants completed a two-week intensive upper limb program utilising the principles of CIMT (Stroke Foundation, 2022; Taub et al., 2006; Taub et al., 2013). Participants in Strathfield completed one-hour of time-on-task supervised training on ten consecutive weekdays, while participants in Brisbane completed four-hours in total in the clinic. All participants were prescribed home exercises. Participants in Strathfield completed

progressively increasing home practice and a transfer package (i.e., behavioural contract and daily completion of the MALQOM).

8.4.3 Outcome measures

The primary outcome for this study is the relationship between the MALAOU, MALQOM, and REACH at pre-intervention, post-intervention, and the change in scores (i.e., post- minus pre-intervention). The results of the MALAOU and MALQOM were reported as the average result. The REACH was reported as the classification level achieved using the algorithm and checklist. A more detailed explanation of the conduct of the MAL-30 and REACH are presented in Chapter 4.8.2 Outcome measures.

8.4.4 Data analysis

Data were entered into REDCap by the research team, downloaded and imported into SPSS for analysis (IBM SPSS Statistics, version 29.0.1.0). Demographic data of the participants are presented as mean, standard deviation and percentages where appropriate. Change in scores was calculated by subtracting the pre-intervention result from the post-intervention result. Two-Sided Paired Sample T-Tests were used to determine the significance of the change in MALAOU, MALQOM and REACH scores. Subgroup analyses were conducted to explore the effect of paretic limb dominance on the scores and correlation of the MALAOU, MALQOM and REACH.

Histograms were used to conduct normality testing of the outcome measures (MALAOU-30, MALQOM-30, and REACH scores) at pre-exercise, post-exercise, and change) which did not demonstrate a normal distribution. Scatterplots were used to visually examine the nature of the relationships between the MALAOU, MALQOM and REACH scores. Spearman rank correlation (rho) was used to examine the correlation between MALAOU, MALQOM and REACH scores at pre-intervention, post-intervention and between the change in results (Akoglu, 2018). A perfect correlation was taken at +/- 1, a very strong correlation between +/- 0.8 and +/- 0.9, a moderate correlation between +/- 0.6 and +/- 0.7, a fair correlation between +/- 0.3 to +/- 0.5 and a poor correlation between +/- 0.1 and +/- 0.2 (Akoglu, 2018). Significance was set at $p < 0.05$.

8.5 Results

8.5.1 Participants

Ten participants (eight male, 80%) aged 63.90 ± 13.89 (range; 34-80) years and 13.80 ± 7.86 (range; 4-28) months post-stroke participated in this study. Characteristics of these participants are presented in Table 8-1. Two participants did not complete the MALAOU assessment at pre-intervention or post-intervention.

Table 8-1 Participant characteristics

Characteristics	**Participants (n = 10)**
Age (years)	63.90 ± 13.89
Sex (F)	2 (20)
Time post-stroke (months)	13.80 ± 7.86
Stroke type (I)	7 (70)
Dominant upper limb affected	5 (50)

Note: Values are mean ± standard deviation or frequency (percentage).

Abbreviations – F: Female, I: Ischaemic stroke.

8.5.2 Motor Activity Log and Rating of Everyday Arm-use in the Community and Home

Table 8-2 presents the average MALAOU and MALQOM results of the included participants. Overall positive improvements were observed following the intervention with improvements in the MALAOU and MALQOM from pre-intervention to post-intervention. Seven participants demonstrated improvements in the MALAOU, and all participants demonstrated improvements in the MALQOM ($p = 0.004$). The MAL MCID of 0.5 points (van der Lee et al., 2008) was achieved by five participants in the MALAOU and four participants in the MALQOM.

Table 8-2 MALAOU and MALQOM results

	Pre-intervention (mean ± SD)	Post-intervention (mean ± SD)	Change (Post-intervention minus pre-intervention) (mean (95% CI))
MALAOU (/5) (n = 8)	1.79 ± 1.41	2.68 ± 1.54	0.89 (0.34 – 1.44)
MALQOM (/5) (n = 10)	1.78 ± 1.55	2.63 ± 1.61	0.84 (0.36 – 1.33)

Abbreviations – MALAOU: Motor Activity Log Amount of Use Scale, MALQOM: Motor Activity Log Quality of Movement Scale.

Table 8-3 presents the REACH results of the included ten participants at pre-intervention and post-intervention. Results are presented as proportions of the population who recorded each level of the REACH at the included timepoints of this study. The mean REACH score was 2.60 ± 1.35 and 2.9 ± 1.37 at baseline and post-intervention, respectively. The mean change in REACH score following the intervention was 0.30 ± 0.82 (p = 0.279).

Table 8-3 REACH results at pre-intervention and post-intervention

	Baseline	Post-intervention
Level 0	1 (10)	1 (10)
Level 1	1 (10)	0 (0)
Level 2	2 (20)	2 (20)
Level 3	3 (20)	4 (40)
Level 4	3 (20)	2 (20)
Level 5	0 (0)	1 (10)

Note: Values are frequency (percentage).

Six participants (60%) reported no improvement in paretic limb use (i.e., two participants at Level 4, two participants at Level 3, one participant at Level 2, and one participant at Level 0) and three (30%) participants reported improvement. The MCID of increase of one level was achieved in 30% of participants (Simpson et al., 2013). Figure 8-1 presents the change in

REACH results graphically. Post-modified-CIMT REACH scale scores relative to pre-modified-CIMT REACH scale scores. On the Y axis is the post-intervention result, and the pre-intervention result is presented on the X axis. Dots on the diagonal represent no change, dots above demonstrate improvement, dots below indicate a decrease in score.

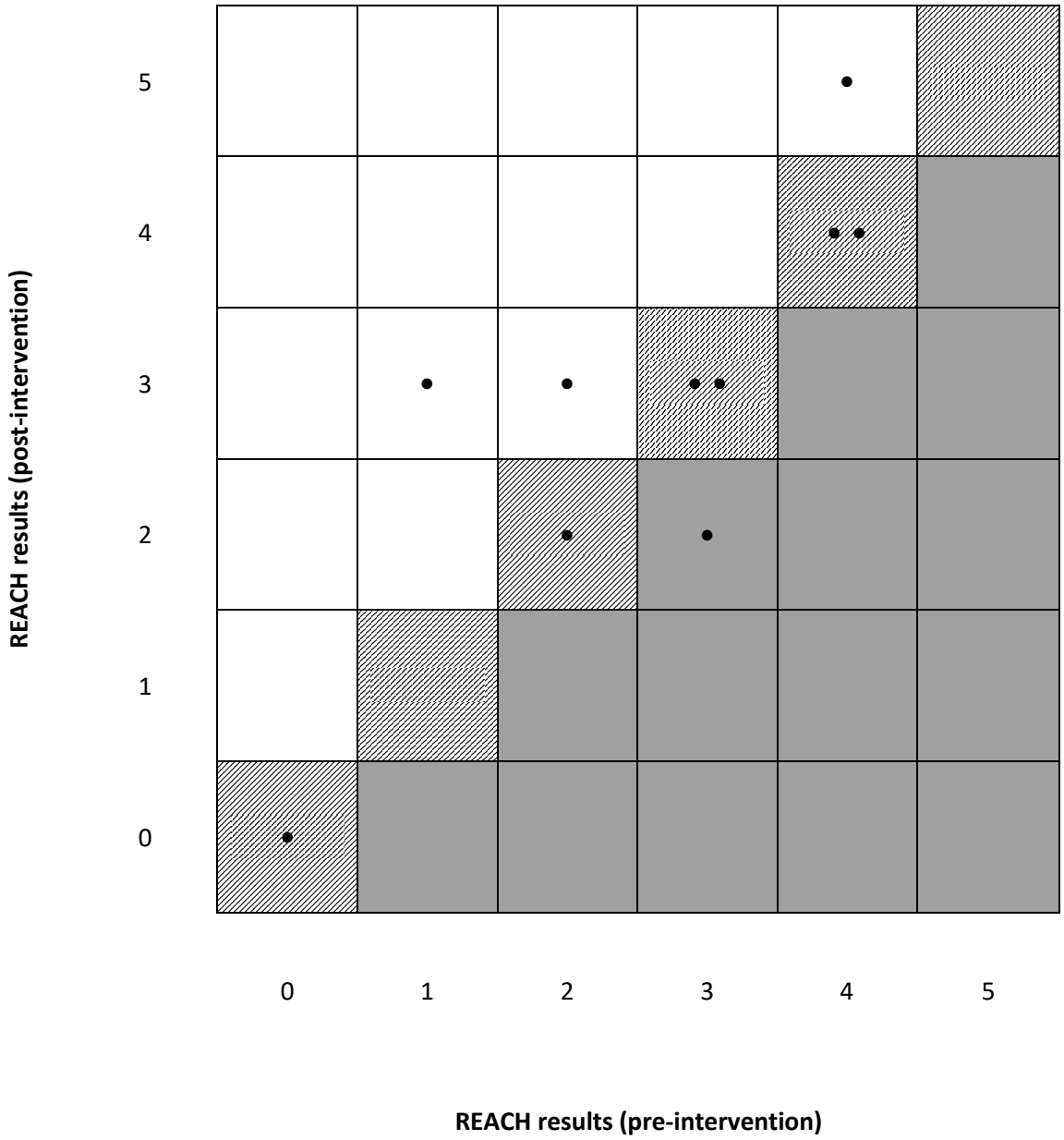


Figure 8-1 Comparison of pre- and post-intervention REACH results

8.5.3 Correlation between Activity Log and Rating of Everyday Arm-Use in the Community and Home

Table 8-4 presents the correlation coefficients between the average MALAOU and MALQOM and the REACH. Scatterplots of the relationships are displayed at pre-intervention (Figure 8-2), post-intervention (Figure 8-3) and change (Figure 8-4).

Table 8-4 Correlation of MAL-30 to REACH

	Timepoint	**Spearman rank correlation coefficient**
MALAOU (n = 8)	Baseline	rho = 0.482
	Post-intervention	rho = 0.294
	Change (Post-intervention minus baseline)	rho = -0.140
MALQOM (n = 10)	Baseline	rho = 0.717*
	Post-intervention	rho = 0.566
	Change (Post-intervention minus baseline)	rho = 0.021

Abbreviations – MALAOU: Motor Activity Log Amount of Use Scale, MALQOM: Motor Activity Log Quality of Movement Scale.

* Significant correlation p = 0.02

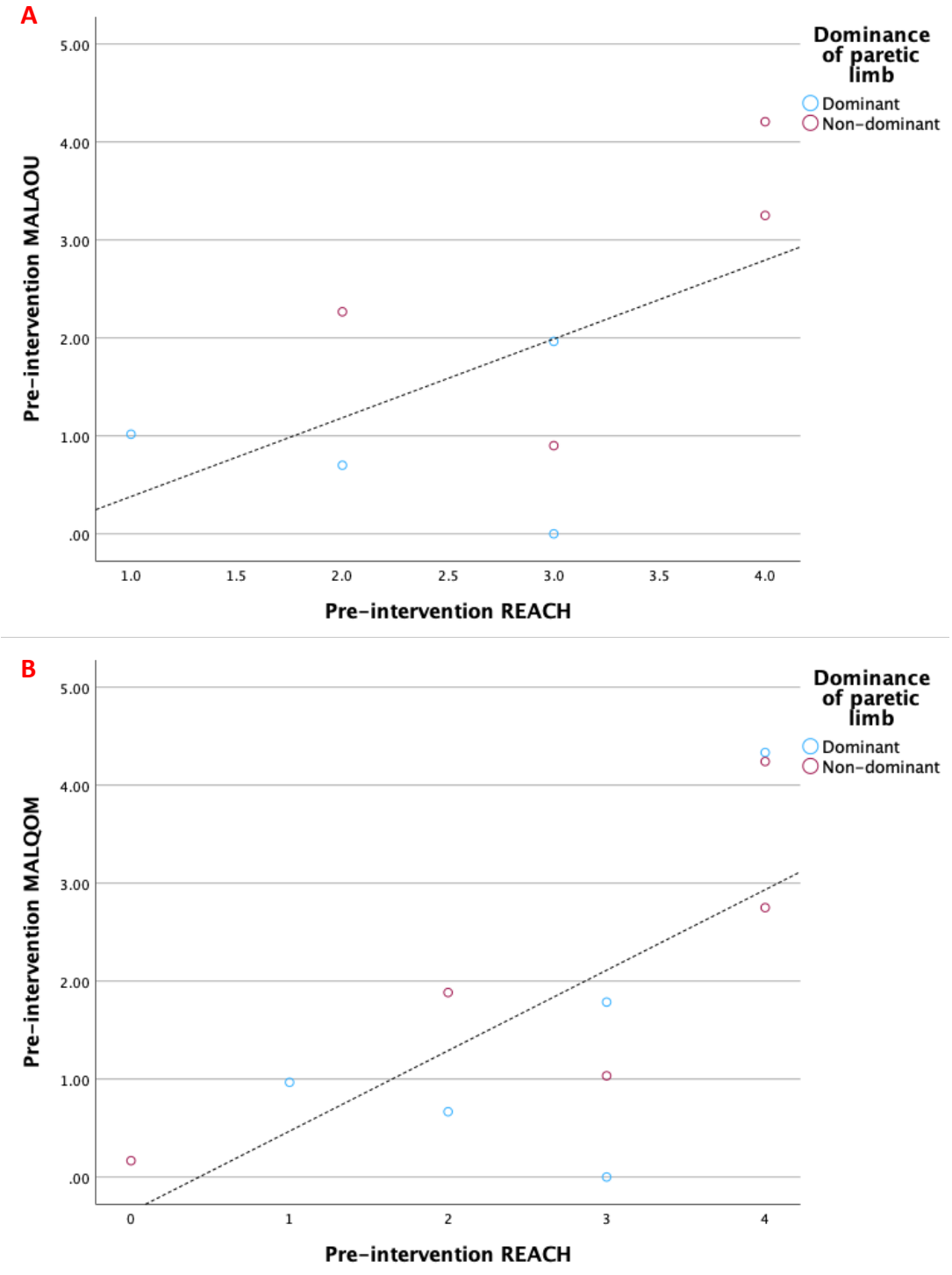


Figure 8-2 Scatterplot of relationship between: A) MALAOU and REACH and B) MALQOM and REACH at pre-intervention

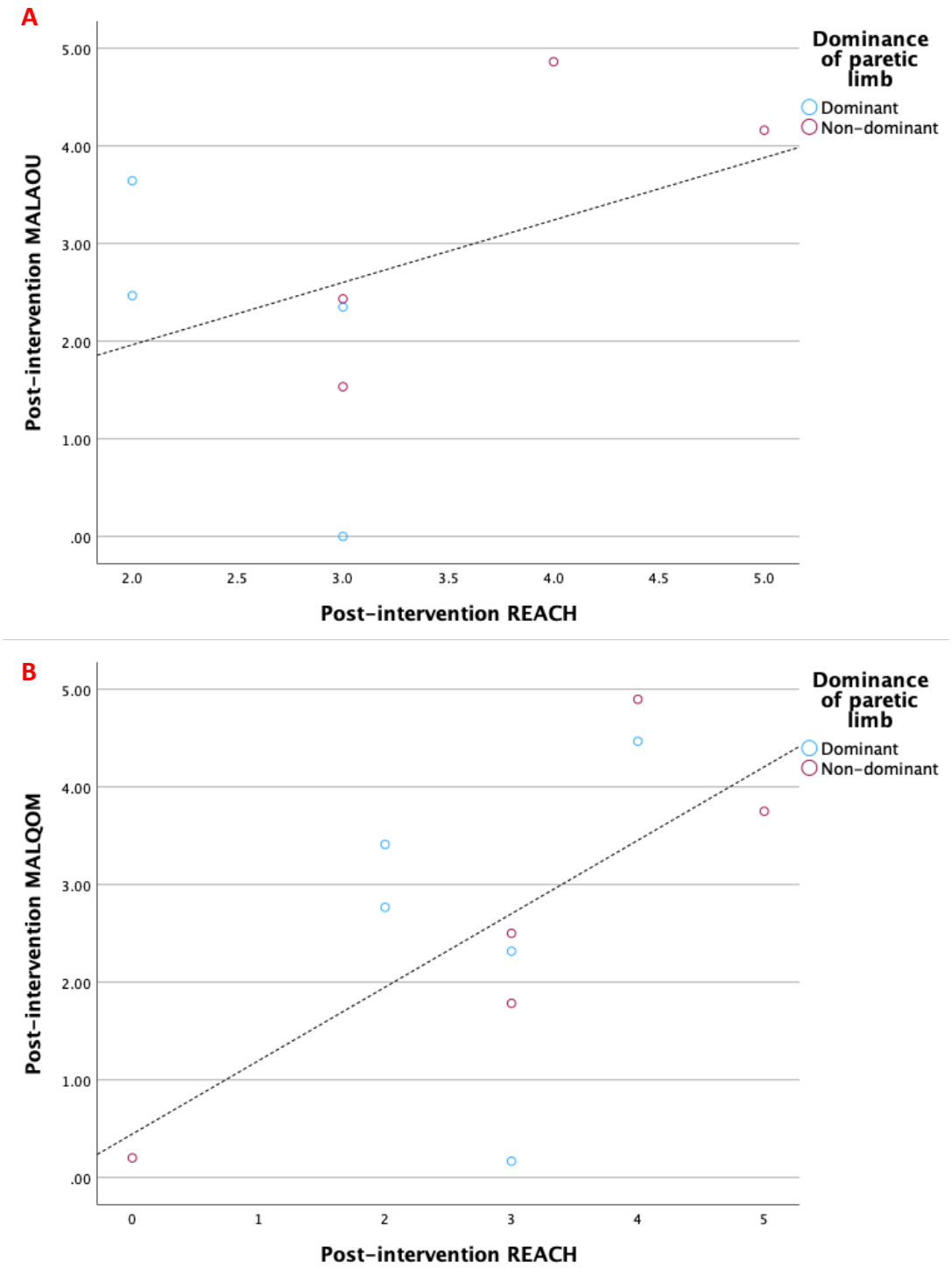


Figure 8-3 Scatterplot of relationship between: A) MALAOU and REACH and B) MALQOM and REACH at post-intervention

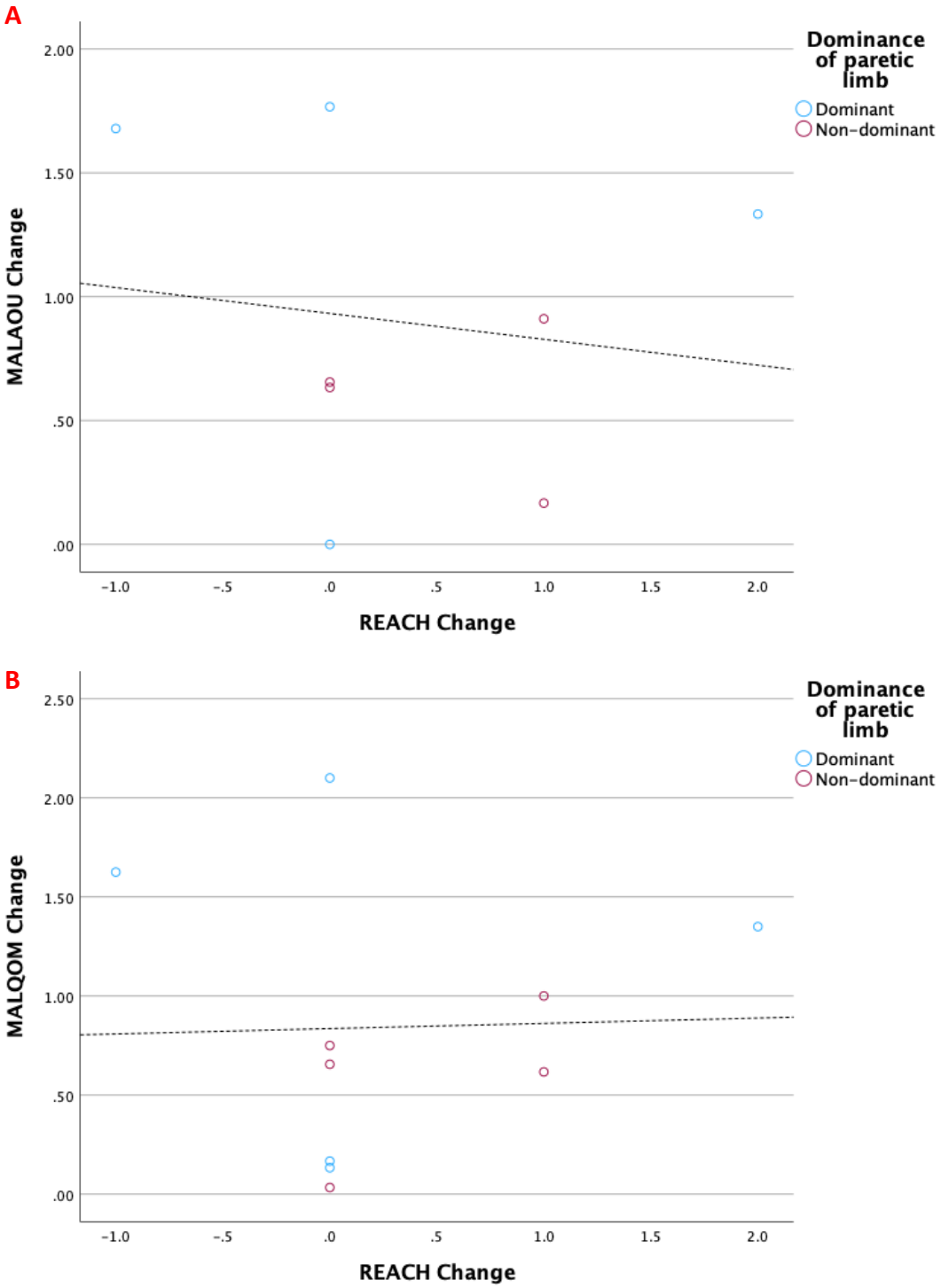


Figure 8-4 Scatterplot of relationship between: A) MALAOU and REACH and B) MALQOM and REACH change

When examining the correlation between the MALAOU and REACH, a fair, not statistically significant correlation was observed at baseline (rho = 0.482, p = 0.227). A poor, not statistically significant correlation was observed between the MALAOU and REACH at post-intervention (rho = 0.294, p = 0.480). A poor, non-statistically significant inverse correlation

was demonstrated when comparing the change in results of the MALAOU and REACH (rho = -0.140, p = 0.740).

When examining the correlation between the MALQOM and REACH, a moderate, statistically significant correlation was observed at baseline (rho = 0.717, p = 0.02). A fair, not statistically significant correlation was observed between the MALQOM and REACH at post-intervention (rho = 0.566, p = 0.088). A poor, non-statistically significant correlation was demonstrated when comparing the change in results of the MALQOM and REACH (rho = 0.021, p = 0.955).

8.6 Discussion

This cross-sectional study demonstrated a statistically significant correlation between the MALQOM and REACH at pre-intervention. No correlation was observed between the MALAOU and REACH at pre-intervention. There was no correlation between the MALAOU, MALQOM, and REACH following a mCIMT program. A fair correlation coefficient was found between the MALQOM and REACH following the mCIMT program. No correlation was found when examining the change in the results of the MALAOU, MALQOM and REACH.

Overall, the MAL-30 does not appear to have a relationship with the REACH in the current study. A strong correlation was found between MALAOU 14-item scale and REACH in a study of 96 people with stroke (mean 7.8 years post-stroke) (Simpson et al., 2013). Participants in both studies were similar in age and recorded similar average MALAOU results at pre-intervention (i.e., mean 1.9 versus 1.79), however no correlation was identified in the current study. This differing correlation may be associated with the use of the MALAOU 30-item scale instead of the MALAOU-14 in the current study. The main difference between the two scales is the inclusion of additional items pertaining to ADLs considered accomplishable by people with stroke with more significant impairment of the paretic upper limb (Taub et al., 1993). Therefore, the MAL-30 may be more sensitive to impairment severity, and subsequently impacted the correlation identified in this study. Regardless, the MALAOU is an examination of functional activity as self-reported by the participant, which aligns with the objective and information collection method of the REACH (Simpson et al., 2013).

The relationship between the MALQOM and REACH has not previously been explored. The current study found a moderate correlation at pre-intervention, though no correlation was found post-intervention or associated with the change in scores. The MALQOM is completed as part of the mCIMT transfer package (McNulty et al., 2015; Wolf et al., 2006), allowing participants to identify methods to increase amount and quality of paretic limb use through discussion with the therapist (McNulty et al., 2015; Taub et al., 1993; Taub et al., 2006; Taub et al., 2013). It is proposed that the daily completion of the MALQOM during the intervention may increase participant problem-solving and goal-setting due to development of strategies to increase the quality of task completion (McNulty et al., 2015), and therefore the score provided at re-assessment. Two participants within this study completed the MALQOM daily, however, these participants recorded the smallest improvements in the MALQOM at post-intervention, suggesting perhaps daily completion may not increase the quality of paretic upper limb use. Alternatively, the reliability of the REACH has not been assessed when completed without the assistance of the therapist, which may make it difficult to replace the MALQOM within the transfer package.

The MAL and REACH are both self-reported measures of upper limb capacity outside a clinical setting and are therefore open to participant interpretation. While the MAL asks participants for a response in relation to the use of their paretic limb prior to stroke, many participants provide a response based on a comparison of the paretic and non-paretic at the time in question (Bhatnagar, et al., 2020). Therefore, issues of neglect and learned non-use may reduce MAL results, despite positive results in clinical assessments (e.g., Fugl-Meyer Assessment Upper Extremity subscale) (Bhatnagar, et al., 2020). Within the current study, numerous participants reported at pre-intervention scores of zero or voiced the task was avoided, however high scores (e.g., ≥3) were reported at post-intervention. The large perceived increase in use and quality of movement may be attributed to the attention brought to the use of the paretic limb, or the discussion with the therapist recommending they trialled the activity more frequently during the intensive upper limb therapy program. This may skew the change in measures identified, and therefore affect the correlation observed between the MAL-30 and REACH.

The REACH is a shorter assessment, which may reduce clinician and participant burden in the clinical environment. The REACH takes approximately five minutes to complete (Simpson et al., 2013), however the MAL-30 takes much longer due to the inclusion of the two scales. The REACH also provides an algorithm and checklist to ensure the use of the paretic limb is classified in the correct level (Simpson et al., 2013). Alternatively, a script and set scoring (i.e., 0 to 5, with the inclusion of half scores) is provided to complete the MALAOU and MALQOM, however considerable probing is required to collect the necessary information (Taub et al., 2011). The MALAOU and MALQOM allow responses to be 'not applicable', removing the item from the calculation of the score if the activity is considered 'impossible' to complete (Taub et al., 2011). Such an item may be removed if the task is not relevant to the participant (e.g., combing hair if the participant has none). However, the instructions of the MAL outline the item should not be listed as 'not applicable' unless deemed truly impossible and should not be removed if too difficult or inconvenient for the participant to complete (Taub et al., 2011). Instead of quantifying frequency or quality of use as in the MAL, the REACH examines upper limb use on a scale which progresses in the complexity of the task (Simpson et al., 2013). Therefore, further examination of the correlation between the MAL-30 and REACH is required before the REACH can be used as an alternative to the MAL in clinical practice.

8.6.1 Limitations

The MAL-30 and REACH are self-reported measures of paretic upper limb use (Simpson et al., 2013; Uswatte et al., 2006). While the MAL is considered reliable to assess upper limb use in mild-to-moderate stroke, self-reported MALAOU responses may have limited reliability (Uswatte et al., 2005). A small sample size was used in this study due to difficulties with recruitment because of the Covid-19 pandemic. The suspension of research due to Covid-19, and the follow-on impact of the pandemic on staff turnover at participating hospitals comprised the capacity to recruit a sufficient sample size of people with stroke to participate in the proposed intervention (Study 5;Chapter 9). In addition, the CIMT clinic run by ACU was only conducted in the Brisbane campus which further limited the number of potential participants to be recruited. The small sample size included in this study did not allow the analysis of impact of hand dominance on the correlation between the MALAOU,

MALQOM and REACH. The assessors used in this study were exercise physiologists and student occupational therapy students, trained by senior therapists in the implementation of the MALAOU, MALQOM and REACH. The potential inexperience of the assessor may reduce the reliability of the results collected. For example, MAL-30 results of some participants indicated tasks were completed independently, with similar quality to their pre-stroke capacity. However, the REACH result indicated the need for assistance, rather than full use. This discrepancy may also be linked to the fact that some tasks can be completed independently while others require assistance, and the REACH groups all tasks together, or that the REACH utilises separate scales based upon the dominance of the paretic limb while the MAL-30 does not. Females were underrepresented in this study, accounting for 20% of the participants, which is consistent with existing stroke trials (Carcel et al., 2021; Strong et al., 2021). Evidence suggests that while stroke is more common in men, females experience more severe stroke at an older age of onset and higher levels of dependence for ADLs (Gular et al., 2022; Liljehult et al., 2021). Access to clinic sites may be a potential barrier to participation for females (Carcel & Reeves, 2021). Few female participants were identified from the recruitment hospital in NSW, which may demonstrate potential bias from recruiters (Carcel & Reeves, 2021). Therefore, the small sample of females included in this study may impact the generalisability of the results collected.

8.6.2 Future directions

Further research is needed to explore the original research questions investigated in a larger cohort. Based upon MALQOM results from existing literature (McNulty et al., 2015), a minimum sample size of 15 participants is required to detect change in the MALQOM-30. Future studies should include a more comprehensive participant demographic, recruiting participants across the spectrum of recovery, stroke type, sex, and paretic limb dominance. Studies must also explore the intra- and inter-rater reliability of the MALAOU, MALQOM and REACH to ensure clinical utility between timepoints and assessors. While the use of a blinded assessor will reduce the risk of bias (Higgins et al., 2022), this is not reflective of real-world clinical practice. Future studies should explore test-retest and intra-rater reliability to ensure accuracy in a clinical setting.

8.7 Conclusion

A moderate statistically significant correlation was observed between the MALQOM and REACH at pre-intervention, but no statistically significant correlation was observed at post-intervention or when comparing the change in results. No significant correlation was observed between the MALAOU and REACH at any timepoint. More research is needed to determine if the REACH can be used as an alternative to the MAL-30 in clinical practice.

8.8 Implementation of this evidence in this program of research

While this pre-post intervention study included a small sample size, the REACH is a suitable outcome measure to be used in the RCT proposed in Chapter 9 of this thesis. In this study, the MALAOU, MALQOM and REACH will be implemented to further explore the relationship between the MAL and REACH in response to an intensive upper limb therapy program.

Chapter 9 STUDY 5: PERSONALISED EXERCISE FOR PRIMING POST-STROKE (PREPP): PROTOCOL FOR A RANDOMISED TRIAL WITH A HISTORICAL CONTROL

9.1 Preface

Study 1 of this thesis identified the need for high intensity aerobic exercise to facilitate significant increases in BDNF concentration, which may optimise skill acquisition when completed within one-hour of skill training (Thomas et al., 2017). However, no consensus appears to have been reached on the ideal temporal ordering of the exercise, i.e., before or after skill training, to optimise skill acquisition (Nepveu et al., 2017; Roig et al., 2012; Ploughman et al., 2019; Thomas et al., 2016). Much of the evidence in stroke and non-stroke populations conducted aerobic exercise prior to skill training (Mang et al., 2014; Roig et al., 2012). The completion of high intensity aerobic exercise prior to skill training may increase fatigue and reduce the number of repetitions that can be completed during the session, particularly in a stroke cohort (Valkenborghs et al., 2019). Alternatively, the completion of aerobic exercise after skill training may improve long-term memory (Roig et al., 2012) and motor skill retention (Nepveu et al., 2017).

The effect of high intensity aerobic exercise interventions on BDNF concentration have been explored in a chronic cohort (included studies in Study 1, Chapter 5). Given the differing mechanisms of recovery experienced by an individual with stroke across the stroke recovery timeframe (Bernhardt et al., 2017), the effect of high intensity aerobic exercise on BDNF concentration needs to be investigated in people in the subacute phase of recovery after stroke. Therefore, an RCT, the gold standard of research (Hariton & Locascio, 2018), is proposed to explore the effect of a combined HIIT and upper limb therapy program on skill acquisition in a subacute stroke cohort. This study was designed prior to the Covid-19 pandemic lockdowns. Therefore, this RCT has not been implemented within this program of research due to difficulties with participant recruitment and the completion of face-to-face research. Instead, the current draft of the RCT is presented, with the intention of further refinement through co-design with people with stroke prior to implementation.

9.2 Abstract

Objective. The primary aim of this study is to investigate the effect of the timing of the delivery of High Intensity Interval Training (HIIT) relative to the delivery of Modified Constraint-Induced Movement Therapy (mCIMT) on upper limb motor-function post-stroke.

Methods. This is a single-blinded randomised trial with an historical control. Participants will undergo a six-week individualised exercise program. Participants will be randomised into one of two interventions: HIIT then mCIMT (Group 1) or mCIMT then HIIT (Group 2). The duration for each intervention will be 2-weeks. Historical control completed the two-week mCIMT only.

Trial outcomes. The primary outcomes of this trial are Fugl-Meyer Assessment Upper Extremity subscale scores and BDNF concentration. Assessments will be completed at baseline (Week 0), end of six-week exercise (Week 6), end of combined intervention (Week 8) and one-month follow up (Week 12).

Sample size. A minimum sample size of 28 participants is required based on historical control Fugl-Meyer Assessment Upper Extremity subscale results.

Analysis. Repeated measures ANOVA with an effect of time and pairwise comparisons will be used to establish the effect of exercise training on BDNF concentrations.

Discussion. Results will indicate the optimal ordering of a combined HIIT and mCIMT intervention to improve Fugl-Meyer Assessment Upper Extremity subscale scores post-stroke. This trial will also identify if the combined intervention is superior to mCIMT only.

Trial registration. This trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622000092796).

9.3 Introduction

More than 475,000 people are currently living with the lasting effects of stroke in Australia (Deloitte, 2020), of which 72% experience some form of upper limb impairment (Stroke Foundation, 2020). Upper limb impairments persist long-term and reduce the individual's ability to complete ADLs (Molle Da Costa et al., 2019) reducing functional independence, QoL (Kelly et al., 2018) and subjective wellbeing (Pollock et al., 2014).

mCIMT is an evidence-based upper limb therapy proven to elicit significant improvements in motor control, function, and daily use of the upper limb (Shi et al., 2011; Smania et al., 2012; Wu et al., 2007). A two-week program of CIMT comprising 14 days of paretic limb restraint and ten days of intensive practice (i.e., six hours per day) can improve paretic limb motor function (Taub et al., 1993). A modified program of CIMT (mCIMT) utilising 14 days of paretic restraint and ten days of supervised and unsupervised intensive practice also improves paretic upper limb motor function and quality of movement (McNulty et al., 2015). Therefore, a two-week program of intensive upper limb therapy would be expected to be sufficient to elicit positive benefits in paretic upper limb use in people with stroke. Upper limb motor rehabilitation optimises neuroplasticity within the brain post-stroke, a process whereby the brain adapts in structure and function (Cramer et al., 2011). One biomarker of neuroplasticity is BDNF (Balkaya & Cho, 2019), associated with the attenuation of neuronal injury and brain damage repair (Liu et al., 2020). Post-stroke, lower BDNF concentrations are associated with poorer long-term functional prognosis (Wlodarczyk et al., 2021). Due to the positive relationship between BDNF and synaptic plasticity (Liu et al., 2020), BDNF is considered a critical mediator of motor learning (Ploughman et al., 2009), with increased functional outcomes demonstrated with higher concentrations (Berretta et al., 2014).

BDNF is secreted in an activity-dependent manner, with greater concentrations identified following exercise completion (Knaepen 2010). The systematic review within this thesis (Study 1, Chapter 5) found that a program of high intensity aerobic exercise such as HIIT demonstrated a very large, significant increase in BDNF concentration. Lactate, a blood marker which increases as exercise intensity increases (Schiffer et al., 2011) is proposed to be produced in the FNDC5/BDNF metabolic pathway (El Hayek et al., 2019; Mueller et al., 2020). The FNDC5/BDNF pathway is also associated with BDNF production, meaning the upregulation of one biomarker may result in the upregulation of the other as a result of exercise. To the best knowledge of the research candidate, no research has explored the relationship between lactate and BDNF concentration in a stroke cohort. While Study 3 (Chapter 7) did not demonstrate a correlation between lactate and BDNF in a mixed-sex healthy cohort, further exploration of the relationship between these biomarkers is required in a stroke cohort (Gonzalez et at., 2018).

As demonstrated in Study 2 (Chapter 6), people with stroke are interested in participating in HIIT interventions. HIIT may also be combined with upper limb rehabilitation interventions to optimise functional recovery post-stroke. Valkenborghs and colleagues (2019) demonstrated improvements in upper limb activity with a combined HIIT and task-specific training program. However, fewer upper limb repetitions were completed in the combined intervention group (i.e., 208 ± 8 repetitions in the task-specific training group versus 158 ± 49 repetition in the HIIT and task-specific training group) (Valkenborghs et al., 2019). The reduced upper limb repetitions completed may be associated with reductions in cardiorespiratory fitness evident following stroke (Ploughman & Kelly, 2019), or exertional fatigue attributed to the completion of HIIT prior to the upper limb therapy. It may be proposed that a program of HIIT prior to the commencement of the combined intervention could facilitate improvements in cardiorespiratory fitness (Crozier et al., 2018), potentially allowing for more upper limb repetitions to be completed during the combined session. Motor learning and memory involves two phases, encoding and consolidation (Craik & Rose, 2012). A necessary level of arousal is needed to facilitate effective learning, however high intensity aerobic exercise undertaken before the skill training and therefore in the encoding phase may inhibit psychomotor task performance (Loras et al., 2020). It is possible that completion of aerobic exercise following skill training may improve skill retention (Nepveu et al., 2017) and potentially avoid additional exertional fatigue. Therefore, the primary aim of this trial is to investigate the effect of the timing of the delivery of HIIT relative to mCIMT (i.e., HIIT before or after mCIMT) on upper limb motor-function post-stroke.

9.4 Methods

A randomised trial with historical control study design will be used to explore the effect of the temporal ordering of HIIT on upper limb motor skill acquisition. Figure 9-1 outlines the CONSORT flow diagram for this study. This study has been approved by Royal Prince Alfred HREC (X21-0432), Royal Rehab Research Governance Office (research governance office for Royal Rehab Private Petersham) (2021-ETH12179) and ACU HREC (2022-2698RC) (Appendix 7-9).

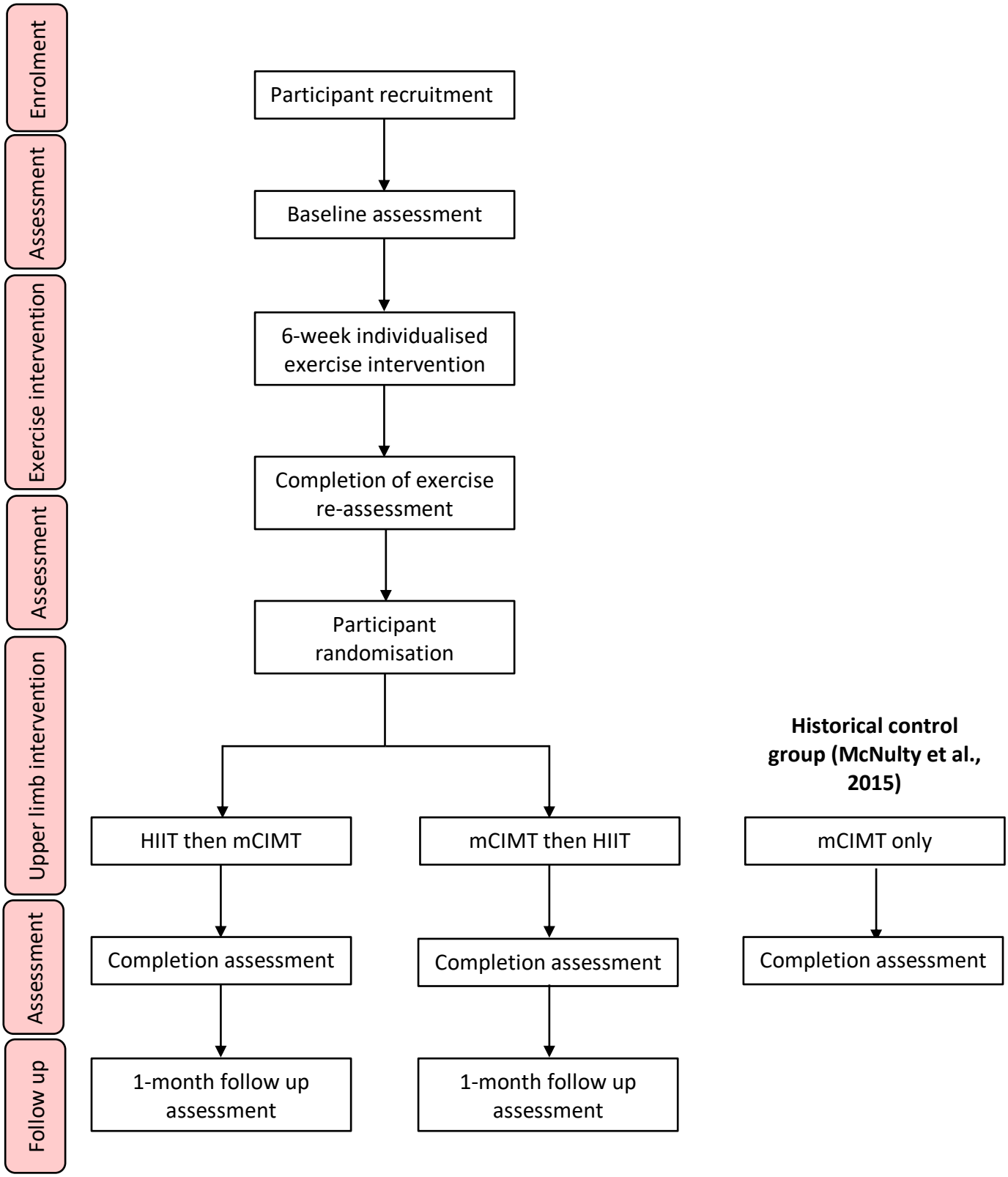


Figure 9-1 CONSORT diagram for proposed randomised controlled trial

9.4.1 Participants and recruitment

Inclusion criteria for participation are: (1) diagnosis of ischaemic or haemorrhagic stroke, (2) diagnosis of upper limb hemiparesis with ≥10 degrees of active movement in the paretic shoulder, elbow, wrist and ≥2 digits, (3) aged ≥ 18 years, (4) understand English, (5) medical clearance to participate in the intervention from a treating medical practitioner, (6) cognitively competent with a Mini-Mental State Examination (MMSE) score of ≥24 out of 30 (Ruchinskas & Curyto, 2003) using the AddenBrooke's Cognitive Examination (ACE-III) (Bruno et al., 2019) and (7) meet Covid-19 vaccination requirements of ACU.

Exclusion criteria are: (1) undertaking any other formal exercise training program during the study period, (2) pregnancy, (3) diagnosis of peripheral neuropathy, significantly affecting sensorimotor function, (4) diagnosis of blood-borne infectious disease, and (5) diagnosis of condition(s) that may limit ability and safety of participation in HIIT (e.g., unstable cardiovascular disease, lower limb conditions).

Participants will be recruited from participating hospitals and via social media posts (e.g., Centre of Research Excellence Stroke Rehabilitation and Brain Recovery newsletter, Facebook, Twitter/X, LinkedIn, the Australian Stroke Foundation website), with enrolment and consent conducted by the research team. A target sample size of 28 participants (i.e., 14 per group) was set based upon Fugl-Meyer Assessment Upper Extremity subscale results published following the intervention of the historical control used in this study (i.e., mCIMT only) (please see Chapter 4.5.3 for more information).

9.4.2 Intervention

All participants will complete a six-week individualised exercise program comprising aerobic (Billinger et al., 2014; Crozier et al., 2018; MacKay-Lyons et al., 2020) and functional exercise (Kelly et al., 2017; Marsden et al., 2017). Exercise will be provided on three weekdays per week, supervised by an exercise physiologist at the Exercise Lifestyle Clinic, ACU, Strathfield. Appropriate exercises will be selected from training recommendations for people with stroke (Askim et al., 2013; Billinger et al., 2014; Kelly et al., 2017; MacKay-Lyons et al., 2020; Marsden et al., 2017) and individualised to each participant. These aerobic and functional circuit exercises will aim to increase cardiorespiratory fitness, functional capacity (Billinger

et al., 2014) and brain health (Wrann et al., 2013). Heart rate, blood pressure, oxygen saturation, shortness of breath, fatigue, and RPE (Borg, 1970) will be monitored before, during and after all supervised sessions as necessary (Liguori et al, 2021). Participant monitoring will ensure the safety of participants and allow for exercises to be regressed or progressed as necessary. HIIT training principles will be progressively introduced during this program to prepare the participant for the HIIT program later in this study.

Upon completion, participants will be randomised to one of two groups: (1) HIIT then mCIMT or (2) mCIMT then HIIT. The combined HIIT and mCIMT intervention will be delivered over a two-week period, with HIIT completed on the non-consecutive weekdays and formal mCIMT sessions completed on ten consecutive weekdays. The HIIT protocol will comprise 25 minutes of 4x4 minute cycling at 85% HR_{peak} interspersed with 3x3 minutes of cycling at 70% HR_{peak} (Askim et al., 2014; Valkenborghs et al., 2019). The mCIMT intervention comprises one-hour of supervised task-oriented training, supplemented with progressively increasing duration of home practice and forced use through the wearing of a mitt on the non-paretic limb for 90% of waking hours (McNulty et al., 2015).

9.4.3 Assessment

The full battery of outcome measures will be conducted by the same treatment blinded assessor at four timepoints (i.e., (1) baseline, (2) completion of six-week exercise program, (3) completion of combined intervention, and (4) one-month follow up). All functional assessments will be filmed for backup. Data from all timepoints will be recorded by the blinded assessor in a purpose-built hard copy data collection form, which will then be transcribed into REDCap (Harris et al., 2009).

9.4.4 Outcome measures

The primary outcome of this trial is the Fugl-Meyer Assessment Upper Extremity subscale to assess upper limb motor function (Fugl-Meyer et al., 1975), as recommended by the SRRR to assess body function and structure (Kwakkel et al., 2017).

Secondary outcomes for this trial include:

1. Additional assessments of upper limb function and use including the Wolf Motor Function Test (Wolf et al., 2001), Box and Block Test (Mathiowetz et al., 1985), Grooved Pegboard Test (Kløve, 1963), MALQOM (Uswatte et al., 2006) and REACH (Simpson et al., 2013).
2. Aerobic fitness quantified using a validated post-stroke submaximal graded exercise test protocol and termination criteria (Yates et al., 2004).
3. Measures of stroke impact including National Institutes of Health Stroke Scale (National Institutes of Health, 2003), Modified Rankin Scale (Bamford et al., 1989), Fatigue Severity Scale (Krupp et al., 1989) and Stroke Impact Scale (Duncan et al., 1999).
4. Blood measures as biomarkers of neuroplasticity including BDNF (Knaepen et al., 2010) and lactate concentrations (Schiffer et al., 2011).
5. Self-reported improvement using a 10-point Visual Analogue Scale (VAS) (McNulty et al., 2015). Intervention satisfaction using a 10-point VAS (McNulty et al., 2015). A score of 1 indicates minimal improvement or satisfaction and a score of 10 indicates upper limb use is at, or near, pre-stroke level and extreme satisfaction, for the respective assessments.

9.5 Data analysis

Demographic data will be tested for normality and presented as mean and standard error, medians and interquartile range and percentages where appropriate. Repeated measures ANOVA with an effect of time and pairwise comparisons will be used to establish the effect of exercise training on BDNF concentrations. One-way repeated measures ANOVAs will be used for functional assessment data. Significance will be taken at $p<0.05$.

A linear mixed-model analysis will be conducted on continuous raw data for all time points (n = 4) providing an intention-to-treat approach. Differences in functional improvement for different therapies, or different motor function classifications will be investigated using additional linear mixed models with an interaction of time and therapy, or time and motor function. The Grooved Pegboard Test and Box and Block Test data will be analysed as dichotomous values using generalized estimating equations because the Grooved Pegboard

Test will only be completed only by patients with high motor function, and the distribution of Box and Block Test scores may be skewed toward values ≤1+. An incomplete Grooved Pegboard Test and Box and Block Test scores ≤1+ will be represented as 0, and a completed grooved pegboard as 1. Repeated measures ANOVAs will be implemented with a factor of therapy (HIIT then mCIMT, mCIMT then HIIT or mCIMT only) to investigate changes in motor function between: (1) baseline and following the individualised exercise program (changes due to increased activity), (2) pre-therapy and post-therapy (therapy efficacy) and (3) post-therapy and six-month follow-up (persistence of improvements). Nonparametric assessment data (data which is not normally distributed) will be logarithmically transformed. Between-group differences in home practice compliance, satisfaction, and self-rated improvement will be tested using Mann–Whitney U tests. Differences considered significant when $p < 0.05$.

9.6 Discussion

A program of HIIT facilitates very large, statistically significant increases in BDNF concentration (Study 1, Chapter 5), however further exploration is needed to demonstrate clear links between BDNF concentration and upper limb motor function recovery. While spontaneous recovery is possible in the early phases of stroke recovery (Bernhardt et al., 2017), a combined intervention such as this may work to reopen this window of recovery to facilitate further improvements in upper limb function (Pollock et al., 2014) due to the increase in neuroplasticity associated with larger BDNF concentrations (Balkaya & Cho, 2019).

Outcomes from this study are hoped to assist with the development of clinical recommendations for post-stroke rehabilitation. At present, HIIT is considered safe and feasible post-stroke to facilitate improvements in cardiovascular health (Boyne et al., 2023; Crozier et al., 2018; Gjellesvik et al., 2021) and greater motor skill retention (Nepveu et al., 2017). However, it appears this intervention is rarely provided in clinical practice. One potential reason may be the exertional fatigue caused which may hinder the success of other interventions (Valkenborghs et al., 2019). Therefore, an exploration of the temporal ordering of HIIT in relation to mCIMT is needed to identify the optimal time to complete HIIT

to facilitate the neuroplastic benefits required, without reducing the number of repetitions of the upper limb needed for mCIMT to be beneficial.

It is expected that moderate improvements in upper limb function will be observed in both Group 1 and Group 2 as indicated by the improvements elicited in the mCIMT only group (historical control) (McNulty et al., 2015). McNulty and colleagues (2015) demonstrated a very large effect (f = 0.89) of the same two-week mCIMT program used in this study on Fugl-Meyer Assessment Upper Extremity subscale scores. It is likely; therefore similar results will be possible with this protocol.

9.6.1 Limitations

The outcome measures proposed in this study are not in complete accordance with the SRRR recommendations (Kwakkel et al., 2017). The WMFT, Box and Block Test and Grooved Pegboard Tests were included in this study to allow comparison to the historical control group who completed these assessments as part of the original protocol (McNulty et al., 2015). Consequently, the Action Research Arm Test was not included in the battery of assessments to reduce the time burden of assessments on participants and the blinded assessor. Difficulties with recruitment were experienced during the time of candidature because of the Covid-19 pandemic and subsequent changes in the business model of the recruitment hospital (i.e., shift of focus away from research involvement to patient safety during the pandemic). Reductions in recruitment rates were reported across the world during the Covid-19 pandemic, with research into the environment prioritised and actions taken to reduce the risk of transmission (Harper et al., 2020; Mitchel et al., 2020). During this time, remote interventions were recommended, however this was not possible given the nature of the interventions and outcome measures of this protocol (Mirza et al., 2022). Recruitment may have also been hindered by the targeted participants and required commitment to be involved in this study. Individuals in the late subacute and chronic phases of recovery were targeted following completion of their rehabilitation at the recruitment hospital. However, given the prolonged time since their stroke, individuals may be less interested in participating in research (Carlstedt et al., 2022) and may have less time to participate. In addition, when speaking with potential participants, the time commitment of

this study and the intensive nature of the combined HIIT and mCIMT program was reported as a barrier to participation.

9.6.2 Future directions

To enhance the application of this protocol, embedding this research in existing upper limb therapy programs, such as the CIMT clinic run at ACU Brisbane, would be beneficial. The use of existing referral and upper limb therapy delivery channels may increase the rate of recruitment and ease of completion of this study. Co-design with people with stroke is also recommended to enhance the feasibility and acceptability of this protocol.

9.7 Conclusion

There is a lack of data from randomised controlled trials to demonstrate the implications of a combined aerobic and upper limb therapy program on the recovery of upper limb motor function following stroke. This trial aims to address this question by comparing the Fugl-Meyer Assessment Upper Extremity subscale outcomes following a program of HIIT then mCIMT versus mCIMT then HIIT versus mCIMT only.

Chapter 10 DISCUSSION AND CONCLUSION

This program of research aimed to explore exercise prescription and uptake post-stroke by 1) identifying optimal exercise training parameters, 2) investigating barriers and facilitators to the prescription and uptake of exercise in clinical practice, and 3) examining the relationship between commonly used outcome measures of neuroplasticity and upper limb function. This chapter will summarise key findings and conclusions, outlining potential clinical implications of this research.

10.1 Key findings of this program of research

This section will summarise the findings of each of the included studies in this thesis.

10.1.1 STUDY 1: Effect of exercise on Brain-Derived Neurotrophic Factor in stroke survivors: A systematic review and meta-analysis

A systematic review with meta-analysis was undertaken to explore the effect of exercise interventions on BDNF concentration in people with stroke. Seventeen studies of a total 687 participants were included in the systematic review, testing BDNF concentration in people with ischaemic and haemorrhagic stroke before and after exercise. A total of 37 separate exercise interventions were conducted across the 17 studies. Twenty-two of the 37 exercise interventions included at least one component of aerobic exercise, while the remaining 15 interventions including non-aerobic interventions. The greatest increases in BDNF concentration were observed following both a single session and a program of high intensity aerobic exercise. The high intensity aerobic exercise interventions provided within the included studies were heterogeneous, with differing frequencies, durations, and types aerobic of exercise provided.

10.1.2 STUDY 2: High Intensity Interval Training Post-Stroke (HIIT-POST): Stroke survivors' and health professionals' views

People with chronic stroke reported an interest in participating in HIIT after stroke. However, few reported involvement in HIIT before or after their stroke. Few health

professionals were confident in prescribing HIIT or had completed formal training in the delivery of HIIT.

Barriers to participation in HIIT reported by people with stroke were a lack of support from health professionals and other people with stroke, and a lack of knowledge of the benefits and safety of HIIT. Facilitators to people with stroke increasing participation in HIIT were supervision of HIIT by trained professionals, and education about the benefits and safety of HIIT after stroke. People with stroke were also interested in education of how HIIT can be personalised to their goals and preferences, as well as their stroke-related impairments.

The main barriers to the prescription of HIIT after stroke, reported by health professionals included a lack of knowledge about what to prescribe and when to commence HIIT after stroke, a lack of motivation of the person with stroke towards HIIT, and uncertainty about how HIIT could be personalised to people with stroke's impairment or level of motivation. Health professionals reported people with stroke require further education to be more confident to participate in HIIT. Health professionals also reported obtaining medical clearance from general practitioners or specialists (e.g., cardiologist) to ensure medical stability and safety to commence a HIIT intervention after stroke would increase their prescription of HIIT.

10.1.3 STUDY 3: Biomarkers for Optimising Rehabilitation and individualised Interventions: BDNF versus lactate

A pre-post intervention study explored the relationship between BDNF and lactate concentrations before and after a submaximal exercise test in a mixed-sex, healthy adult cohort. Significant increases in BDNF and lactate concentrations were observed after exercise, but the biomarkers were poorly correlated with each other pre- and post-exercise, as were the change scores (i.e., pre- to post-exercise). A moderate correlation was evident between BDNF and lactate in participants with the Val66Met polymorphism pre-exercise, but no correlation was observed at any other timepoint. No correlation was observed between BDNF and lactate concentrations at any timepoint in participants without the Val66Met polymorphism. When accounting for sex, a moderate inverse correlation was

identified pre-exercise for male participants, but not at any other timepoint. No correlation was found between BDNF and lactate at any timepoint for female participants.

10.1.4 STUDY 4: Relationship between the Motor Activity Log and the Rating of Everyday Arm-Use in the Community and Home in a post-stroke population

A cross-sectional study explored the relationship between the MAL-30 (i.e., MALAOU and MALQOM) and REACH before and after a two-week intensive upper limb therapy program in a stroke cohort. Improvements were observed in the MALAOU, MALQOM and REACH scores following the upper limb therapy program (i.e., higher average and level recorded at post-intervention when compared to pre-intervention, respectively).

The MALQOM and REACH were moderately correlated at pre-intervention. No other correlations were found between any measure at any timepoint, or when comparing change scores. The lack of correlations observed continued even when accounting for paretic upper limb dominance.

10.2 Clinical implications of this program of research

Several clinical implications have been raised from this program of research, including:

1. People with stroke can benefit from high intensity aerobic exercise.
2. People with stroke and health professionals are interested in participating in, and prescribing, HIIT intervention, respectively.
3. Further education delivered to health professionals about the recommendation and/or prescription of HIIT might increase use in stroke rehabilitation.
4. Further research is needed to confirm the use of lactate as a biomarker of neuroplasticity.
5. The REACH may be a useful upper limb outcome measure to identify meaningful change as a result of intensive upper limb therapy.

10.2.1 People with stroke can benefit from high intensity aerobic exercise

The systematic review and meta-analysis (Study 1, Chapter 5) demonstrated high intensity aerobic exercise can increase BDNF concentration. BDNF concentration is an emerging

outcome of interest due to its ability to potentially temper brain injury and repair brain damage (Liu et al., 2020). High BDNF concentrations have been linked to increased neuroplasticity (Balkaya & Cho, 2019; Liu et al., 2020) and improved functional outcomes (Wang et al., 2017). Although no MCID has been established within the literature for changes in BDNF concentration post-stroke, the potential role of increasing BDNF for people post stroke remains important. This has potential implications for stroke recovery and suggests further research into measuring and investigating mechanisms to increase BDNF concentration via therapeutic interventions is necessary.

The systematic review and meta-analysis (Study 1) found a large increase in BDNF concentration was observed following acute bouts of high intensity aerobic exercise (i.e., a symptom-limited graded exercise test or a single session of HIIT). While a single session of high intensity exercise is sufficient to produce increases in BDNF concentration, larger increases in BDNF concentration are observed following a program of high intensity aerobic exercise (Study 1). High intensity aerobic exercise may be difficult to achieve and sustain in a stroke population (Boyne et al., 2023), and therefore an individual may not be able to tolerate a program of high intensity aerobic exercise, at least initially. However, as the systematic review and meta-analysis shows, even a single session of high intensity aerobic exercise can elicit increases in BDNF concentration. As the person with stroke regains fitness and function, the frequency of HIIT sessions can be increased as tolerated, with the participant then benefiting from both acute and chronic effects of HIIT on BDNF concentration.

HIIT is proven to be a safe and feasible intervention for people with stroke, with no serious adverse events reported (Anjos et al., 2022; Boyne et al., 2016; Gjellesvik et al., 2020). Included participants in these studies were screened for safety prior to the intervention, were a minimum of three months post-stroke (Boyne et al., 2016; Boyne et al., 2023), were able to walk independently (Boyne et al., 2016; Boyne et al., 2023; Crozier et al., 2018; Gjellesvik et al., 2021), and were not diagnosed with an unstable cardiac condition (Boyne et al., 2016; Boyne et al., 2023). Therefore, at present, the safety of HIIT can only be generalised to people with stroke in the late subacute phase who do not have an unstable cardiac condition and are well functioning (e.g., able to independently mobilise).

Of the 17 studies included in the systematic review and meta-analysis (Study 1), no adverse events were reported in six studies, with the remaining 11 studies not reporting adverse events. While ongoing participation in structured exercise training is recommended by clinical guidelines, the evidence supporting the inclusion of HIIT in stroke rehabilitation suggests an overall HIIT dose ranging from 12 to 24 hours is necessary for benefits in BDNF concentration to be observed. Therefore, while the exact duration of exercise required for a person with stroke to increase BDNF concentration remains unclear, it is reasonable to suggest that the more hours completed, the better.

It is not clear if a there is a single mode of exercise that optimises increases in BDNF concentration. The greatest increase in BDNF concentration were seen with treadmill walking. Treadmill walking in people with stroke has been demonstrated to increase walking speed and endurance (Anjos et al., 2020; Nascimento et al., 2021), and is arguably task-specific practice for walking. Following stroke, task-specific practice is suggested to be the best way to learn a task (Bayona et al., 2005), facilitating to neuroplastic changes (Cramer et al., 2011). The Stroke Foundation strongly recommend treadmill walking as a modality to provide people with stroke with repetitive walking practice (Stroke Foundation, 2022). However, the mode of high intensity exercise undertaken by people with stroke is likely dependent on the types and levels of impairments experienced. Other modes of exercise i.e., cycle ergometry, should be considered viable modes of striving to achieve high intensity exercise targeting increases in BDNF concentration.

Aside from the increased BDNF concentration elicited by HIIT, other benefits from HIIT programs have been described in previous research. Improvements in cardiorespiratory fitness have been found following HIIT when compared to moderate intensity continuous aerobic exercise (Anjos et al., 2020; Wiener et al., 2019). Low aerobic fitness is common following stroke (Ploughman & Kelly, 2016), and may limit walking speed and endurance (Smith et al., 2012). HIIT programs have also shown to improve walking speed (Anjos et al., 2020; Wiener et al., 2019) and balance (Anjos et al., 2022). Within the systematic review and meta-analysis by Anjos and colleagues (2020), greater benefit in cardiorespiratory fitness, walking speed and balance were evident following the completion of a treadmill HIIT program. However, improvements in cardiorespiratory fitness are also possible following a

cycle ergometer HIIT program. Improvements in quality of life (Soh et al., 2022) and increased quality-adjusted life years (Hornby et al., 2022) were also found. Therefore, HIIT is beneficial in promoting positive improvements in parameters other than neuroplasticity and should be further encouraged within stroke rehabilitation.

Practically, the integration and recommendation of HIIT after stroke will vary amongst people with stroke due to an array of personal factors (e.g., stroke impairment, exercise tolerance, motivation, goals). Table 10-1 outlines considerations for the clinical application of HIIT after stroke based upon existing literature and findings from this program of research, with particular emphasis on the use of HIIT to increase BDNF concentration.

Table 10-1 Considerations for the clinical application of HIIT after stroke

Area of prescription	Considerations for HIIT after stroke from existing literature	Considerations for HIIT identified within this program of research
Health screening	Medical clearance is required (Macko, 2016). Guidance from an appropriate allied health or medical professional required prior to commencement (APSS, version 2, ESSA, 2019).	Medical clearance should be sought. A clear outline of the HIIT program should be provided to allow the medical practitioner (e.g., GP, cardiologist) to provide informed clearance.
Physiological assessment	Maximal graded exercise test with ECG monitoring (Boyne et al., 2016). Symptom-limited or submaximal stress test with ECG monitoring (MacKay-Lyons et al., 2020).	Submaximal graded exercise test to calculate exercise intensity. ECG may be conducted during the submaximal graded exercise test to identify cardiovascular concerns.
Time to commence after stroke		More commonly implemented in chronic stroke. Medical clearance preferred prior to commencement.
Frequency of HIIT sessions	2-5 sessions per week for ≥4 weeks, initially allowing three days between sessions for recovery (Crozier et al., 2018). 3 sessions per week for a minimum of 4 weeks (Boyne et al., 2016).	2-3 sessions per week for 12-18 weeks (Hsu et al., 2021). But one session is sufficient to increase BDNF concentration (Boyne et al., 2020) if participant cannot tolerate a program.

Area of prescription	Considerations for HIIT after stroke from existing literature	Considerations for HIIT identified within this program of research
Exercise intensity	<u>'On' period:</u> • 85 – 90% HRR (Crozier et al., 2018). • 90 – 100% VO_{2peak} (Crozier et al., 2018). • 85% HR_{peak} (Askim et al., 2014). • 14 – 16 RPE (Billinger et al., 2014). <u>'Off' period:</u> • 70% HR_{peak} (Askim et al., 2014). • 12 – 13 RPE (Billinger et al., 2014).	<u>'On' period:</u> • Maximal tolerated speed (0%) incline on treadmill (Boyne et al., 2020). • 80% VO_{2peak} (Hsu et al., 2021). <u>'Off' period:</u> • Treadmill stopped (0 km/hr) (Boyne et al., 2020). • 40% VO_{2peak} (Hsu et al., 2021)
Exercise interval duration	<u>'On' period:</u> Between 30-seconds and 3-minutes (Crozier et al., 2018). <u>'Off' period:</u> Between 30-seconds and 4-minutes (Crozier et al., 2018). ** Variation in the ratio of active ('on') to recovery ('off') phase duration, as tolerated by the person with stroke (Boyne et al., 2013).	<u>'On' period:</u> 30-seconds (Boyne et al., 2020). 3-minutes (Hsu et al., 2021). <u>'Off' period:</u> 30 and 60-seconds (Boyne et al., 2020). 3-minutes (Hsu et al., 2021).
Session duration (i.e., duration of all intervals added together)	25 – 30 minutes (Crozier et al., 2018).	25-minutes (Boyne et al., 2020). 30-minutes (plus a 3-minute warm up and cool down) (Hsu et al., 2021).

Area of prescription	Considerations for HIIT after stroke from existing literature	Considerations for HIIT identified within this program of research
Type of modality	Cycle ergometer, Stepper, Treadmill (Crozier et al., 2018).	Treadmill, Stepper (Boyne et al., 2020). Cycle ergometer (Hsu et al., 2021).
Monitoring	<u>Before exercise:</u> Heart rate and blood pressure (Crozier et al., 2018). <u>During exercise:</u> RPE (Crozier et al., 2018). Addition of heart rate and blood pressure if appropriate and/or possible. <u>After exercise:</u> Heart rate and blood pressure (Crozier et al., 2018).	<u>During exercise:</u> Heart rate (Boyne et al., 2020; Hsu et al., 2021). Blood pressure and oxygen saturation (Hsu et al., 2021). RPE and the talk test. Addition of blood pressure if appropriate and/or possible.

Abbreviations – VO_{2peak}: highest oxygen consumption achieved during testing, HRR: Heart rate reserve, ECG: Electrocardiogram, HR_{peak}: Heart rate peak, RPE: Rate of perceived exertion.

10.2.2 People with stroke and health professionals want HIIT interventions

People with stroke, and the health professionals who work as part of the multidisciplinary team in stroke rehabilitation, consider HIIT to provide valuable benefits following stroke (Study 2, Chapter 6).

People with stroke and health professionals report the term 'high intensity' may be off-putting and a barrier to participation in HIIT. Instead, a description of the intervention protocol with increased focus on the interval aspect, describing bouts of relative harder work with active rest periods of lighter work is recommended. The emphasis should be placed on the prescription of exercise intensities that are relative to the capacity of the person with stroke. For example, the following description of HIIT could be provided to a person with stroke by a health professional: *"A program of aerobic exercise where you will be working a little harder for a short time and then working at a lighter pace to recover".*

People with stroke and health professionals also report that more information is needed to facilitate greater participation in, and prescription of HIIT. The development of co-designed resources will ensure the education provided about HIIT aligns with what is wanted (discussed in Chapter 10.3.2). Health professionals reported wanting professional development to increase their understanding of the use of HIIT after stroke which is discussed in Chapter 10.2.3. It may be recommended that the professional development courses are co-designed with health professionals to increase engagement and use of the information provided.

10.2.3 Education is needed for the multidisciplinary team on HIIT following stroke

HIIT is not routinely prescribed in the clinical environment (Boyne et al., 2017). The Australian clinical guidelines recommend cardiorespiratory fitness after stroke (Stroke Foundation, 2022), and HIIT is a model of cardiorespiratory fitness training. Few health professionals included in this study reported undertaking formal training in the conduct of HIIT, with no health professionals reporting specific training for stroke populations. At present, limited formal training exists to support the use of HIIT in stroke rehabilitation. Therefore, structured professional development courses should be developed, which should

consider the various levels of expertise in exercise prescription health professionals currently have. For example, professional development courses should cover education about the prescription of HIIT for professionals with high levels of expertise (e.g., exercise physiologists and physiotherapists) and the reinforcement of the benefits of HIIT for professionals with a scope of practice not including exercise (e.g., occupational therapists or medical practitioners). The inclusion of the information regarding the use of HIIT post-stroke should also be included in tertiary curriculum for exercise physiologists and physiotherapists to promote awareness of this intervention and support for its application in clinical practice.

Professional development courses should be co-designed with health professionals (with expertise with exercise) to ensure appropriate information is delivered. Topics covered should include education on: (a) what HIIT is, (b) the benefits of HIIT after stroke, (c) screening and assessment prior to HIIT, (d) potential HIIT prescription for people with stroke, (e) safety and monitoring during HIIT, and (f) education for people with stroke. Information could be delivered as a lecture (delivered in-person or via an online webinar), in-service or a practical course where health professionals can practice the skills learnt with a peer or volunteer person with stroke. An example of a lecture that could be delivered to the multidisciplinary team to provide education on HIIT for people with stroke is provided in Appendix 12.

The implementation of aerobic exercise training, including HIIT, can be improved through a multidisciplinary approach to stroke rehabilitation, including the involvement of medical and allied health professionals (Inness et al., 2022). People with stroke have reported increased confusion regarding exercise interventions when different messages are provided (e.g., advice to rest versus advised to complete aerobic exercise training). Therefore, a cohesive message about the need for beneficial aerobic exercise (versus physical activity) after stroke should be communicated to all members of the multidisciplinary team.

10.2.4 Further research is needed to confirm the use of lactate as a biomarker of neuroplasticity

Despite the mechanistic associations (El Hayek et al., 2019; Herrera-Lopez & Galvan, 2018; Hu et al., 2021), based upon the evidence presented in Study 3 (Chapter 7) of this thesis, lactate cannot be argued as an alternative biomarker of neuroplasticity due to lack of correlation identified between lactate and BDNF.

While the collection and analysis of peripheral lactate concentration is minimally invasive, easy to collect and relatively cheap, compared to BDNF collection and analysis, the lack of association between the biomarkers before and after exercise in the healthy adult cohort tested in this research suggests these biomarkers cannot be used interchangeably. However, further research is needed both in healthy adults and clinical populations such as people with stroke to confirm. Certainly, lactate analysis may be more feasible than BDNF analysis in clinical practice and peripheral blood collection is within the scope of practice of many allied health professionals (Australian Physiotherapy Association, 2011; Exercise and Sport Science Australia, 2015).

Both lactate and BDNF are responsive to exercise intensity, whereby increases in both were evident following the submaximal graded exercise test (Study 3). If the intensity of exercise is sufficient (i.e., high intensity), increases in lactate (Magistretti & Allaman, 2018) and BDNF concentration (Fernández-Rodríguez et al., 2022; Jiménez-Maldonado et al., 2018; Schmolesky, Webb & Hansen, 2013) are evident. A relationship between BDNF and lactate following a graded exercise test has been reported in a mostly male cohort (Ferris et al., 2007). This was also evident in this program of research in males, but not females, and at pre-exercise but not change scores. Therefore, while lactate may be used as an indicator of exercise intensity to ensure high intensity aerobic exercise is achieved to increase BDNF concentration, lactate does not appear to be a suitable alternative to the measurement BDNF concentration as a biomarker of neuroplasticity in healthy adults.

10.2.5 The REACH may be useful to identify meaningful change as a result of intensive upper limb therapy

It remains unclear from this program of research how useful the REACH is to identify meaningful change in paretic upper limb use following upper limb therapy. In this current study, approximately one-third of participants demonstrated meaningful change meeting the MCID for the REACH following the two-week intensive program while two-thirds of participants reported the same score at post-intervention. The REACH was co-designed with people with stroke, caregivers, and health professionals whereby an improvement of one level is considered a meaningful improvement following therapy (Simpson et al., 2013). Additionally, approximately half of the participants also met the MCID on the MAL-30.

The lack of clear outcome is likely due to the limitations of this study, and further research is required to determine how the REACH can be used in clinical practice, particularly as part of an intensive upper limb therapy program such as mCIMT. Limitations previously discussed (8.6.1 Limitations) include the small sample size and differences in the delivery of the intensive upper limb therapy in this study. The MAL-30 seemed to not be as impacted by these limitations with more participants meeting the MCID, and improvements in the MALQOM reaching statistical significance. One potential reason for this difference in number of participants achieving the MCID may be the scoring structures of the scales. The MALAOU and MALQOM comprise 30-items each scored out of five, allowing for a potential total score of 150 which is then averaged to a score out of five. The REACH utilises a checklist of potential function, scored from zero to five. Thus, large increases are needed in paretic upper limb function to increase the score on the REACH, while only small improvements may be needed to increase MALAOU or MALQOM score.

The REACH appears to have some advantages over the MAL-30 such as taking less time to administer (less than 5 minutes), accounting for hand dominance and the scoring has been determined as meaningful by people with stroke, caregivers, and health professionals (Simpson et al., 2013). Therefore, further research is needed to explore the relationship between the REACH and MAL-30 in a larger cohort.

10.3 Future directions

Findings from the studies within this program of research provide direction for future research. The data presented highlight the need for larger scale and co-designed research studies to optimise the use of HIIT in stroke rehabilitation and determine the relationship between established and proposed outcome measures of neuroplasticity and upper limb function.

10.3.1 Diversity of views of High Intensity Interval Training is needed

Providing personalised HIIT is needed to produce the most benefit for people with stroke. To achieve this, research must be conducted with a diverse sample of people with stroke, including the potential influence of personal factors such as preference for exercise, culture, and language.

The people with stroke included in this program of research (Study 2, Chapter 6) were mostly female in the chronic stage of stroke recovery. To obtain a comprehensive understanding of how to personalise HIIT to individual and stroke-specific factors, a larger and more diverse participant group is needed. A diverse sample would likely increase representation across the stroke population, allowing for greater generalisability and potential for translation to clinical practice. Pre-notification of the study (e.g., phone calls or emails), a shorter questionnaire, more personalised study materials and reminders to complete the questionnaire may increase participation rates, and therefore sample size (Harrison et al., 2019). In addition, recruitment through inpatient rehabilitation facilities where people with stroke may be more attentive and focused on initial recovery, and when multidisciplinary healthcare is utilised may increase participant numbers and diversity.

It is recommended that people with stroke of different ages, with varied previous engagement in exercise including HIIT (i.e., have participated and have not participated), different levels of physical and cognitive impairment, presence or absence of aphasia and different affinities for exercise, as examples, be included in future research. Stroke rehabilitation research has suggested targeting clearly defined subgroups may be useful to build knowledge, and when information from different groups is collated can be applied to a

broader population (Dalton et a., 2023). Within the context of this study, conducting questionnaires and interview for specific sub-groups of people with stroke (e.g., Aboriginal and/or Torres Strait Islander peoples, people who have not completed HIIT previously) and health professionals (e.g., health profession) may be useful to build the sample size, and therefore the generalisability of the barriers and facilitators to HIIT collected.

Similarly, people with stroke of differing language and cultural backgrounds should be included in future studies to explore potential barriers to engagement in HIIT and allow for personalisation of the intervention. The questionnaire and interview script must consider culturally and linguistically diverse points of view or areas of concern to ensure the research team are capturing relevant barriers and facilitators which may differ between cultural and language contexts. This can be achieved through co-design with people with stroke of indigenous or culturally and linguistically diverse communities. Such engagement with lived experts will allow questionnaires or interviews to be culturally and linguistically appropriate (Slattery et al., 2020).

A larger and more diverse population of health professionals are needed to explore the barriers and facilitators to the recommendation and/or prescription of HIIT across the multidisciplinary team. Health professionals of with differing scope of practice, experience level and expertise with exercise is required to allow strategies to be developed to increase the use of HIIT in clinical practice. This may be achieved through the advertising of promotional materials within hospital lunchrooms, newsletter, or email lists for various health professions (e.g., Australian Health Practitioner Regulation Agency, Australian Medical Association) or at relevant conferences such as Smart Strokes or Stroke Society of Australasia.

10.3.2 Development of co-designed High Intensity Interval Training information resources

Resources to provide information about HIIT post-stroke are necessary to increase participation and prescription. Co-design of HIIT resources would ensure the information aligns with what is considered important by the person with stroke, and in an appropriate format for the person with stroke (Pearce et al., 2015; Slattery et al., 2020). Information resources targeted toward people with stroke should utilise co-design approaches to ensure

the interests of the people with stroke are met (Plant et al., 2016). Co-design involving people with stroke (i.e., consumers) in conjunction with health professionals (i.e., providers) will likely minimise any mismatch between advice sought and advice provided (Plant et al., 2016). Information resources should consider the language used to ensure consumers can understand the content. People with aphasia following stroke have specific communication needs (Brady et al., 2020), therefore information resources must be co-designed with people with aphasia to ensure the information is presented appropriately (Rose et al., 2011).

In addition to co-design to support the development of HIIT information resources after stroke, the distribution of resources must also be determined with the assistance of lived experts. The preferred timing (e.g., phase of stroke recovery) and modality of information delivery (e.g., brochures/flyers) should be explored as evidence suggests information too early and in a format undesirable to the individual may be ineffective (Lennon et al., 2013). Resources of different modalities, such as video utilising narration and images, or the use of software that supports a 'read aloud' function for online documents is recommended to increase accessibility for people with aphasia (Shiggins et al., 2022).

10.3.3 Investigating the relationship between neuroplasticity and upper limb measurement variables with a larger sample size

Two studies (Study 3, Chapter 7 and Study 4, Chapter 8) within this program of research explored the relationship between measures of neuroplasticity and paretic upper limb function. Sample sizes that are powered to identify the relationship in outcome measures (i.e., BDNF and MAL-30) are needed before clinical implications can be recommended.

Based on the findings of Study 3 (Chapter 7) of this program of research exploring the relationship between BDNF and lactate concentration, using G Power, with an effect size of 0.58, significance level of 0.05 and 80% power, a minimum sample size of 26 healthy adults need to be recruited to quantify the relationship between BDNF and lactate concentration following a submaximal graded exercise test. Due to the potential impacts of the presence of the Val66met polymorphism (Lemos et al., 2016) and sex (Wei et al., 2017) Future research must explore the relationship between BDNF and lactate concentration in a stroke

cohort to assist with the personalisation of stroke rehabilitation. To participate in such an investigation in a stroke cohort, people with stroke would need to be older than 18 years of age, have experienced a confirmed ischaemic or haemorrhagic stroke, have the capacity to provide informed consent and the capability to complete a submaximal graded exercise test. People with a blood-borne infectious disease or who are pregnant would be excluded from this study. Based on BDNF concentration data from a graded exercise test (Boyne et al., 2020), using G Power, with an effect size of 0.5, significance level of 0.05 and 80% power, a minimum sample size of 45 people with stroke is needed. Therefore, a minimum sample size of 54 people with stroke should be recruited to account for 20% drop out.

To further explore the relationship between the MAL-30 and REACH following a two-week intensive upper limb program a minimum sample size of 36 people with upper limb hemiparesis after stroke would need to be recruited. This is based on the findings of Study 4 (Chapter 8) of this program of research and is inclusive of both the MALAOU and MALQOM scales. To quantify the relationship between the MALQOM and REACH, with an effect size of 0.54, significance level of 0.05 and 80% power, a minimum sample size of 36 people with upper limb hemiparesis after stroke is required, accounting for 20% drop out. Participants would need to include people with varying stroke aetiology (ischaemic, haemorrhagic), gender, time post stroke, hand dominance and paretic side.

10.3.4 Exploring HIIT to improve neuroplasticity after stroke

A RCT is proposed in Chapter 9 of this thesis to explore the effect of a combined HIIT and upper limb therapy intervention on paretic upper limb function after stroke. As identified within the systematic review and meta-analysis (Chapter 5), a program of HIIT on a cycle ergometer demonstrated a large increase in BDNF concentration (Hsu et al., 2021).

A program of high intensity aerobic exercise, such as HIIT, may improve motor skill acquisition when completed in close temporal proximity to motor skill training (Thomas et al., 2017). Undertaking HIIT to increase BDNF concentration before skill training (e.g., upper limb therapy) may improve upper limb motor function (Valkenborghs et al., 2019). Although, it is possible that undertaking HIIT before upper limb therapy may elicit high levels of volitional fatigue, reducing the number of upper limb repetitions that can be

completed (Valkenborghs et al., 2019). It has also been hypothesised that undertaking HIIT after skill training may increase the efficacy of skill training (Nepveu et al., 2017) and improve long-term memory (Roig et al., 2012). It is unclear which timing is preferential. The proposed RCT aims to identify the effect of the timing of HIIT in relation to the intensive upper limb therapy program on BDNF concentration and functional outcomes of the upper limb.

People with stroke and health professionals who partook in Study 2 (Chapter 6) expressed an interest in HIIT due to its capacity to facilitate improvements in stroke recovery as well as physical and mental health post-stroke. Anecdotal feedback from participants in a pilot of this protocol expressed concerns in relation to the time burden of the intervention, fatigue elicited by the intense nature of the exercise and upper limb intervention, as well as the implications of this fatigue on daily life. The proposed protocol will be amended through a process of co-design with people with stroke to assist in sustaining the goals of the intervention beyond completion of the project and increase meaning for the consumer (Andersson, 2017; Jagosh et al., 2012). The co-designed intervention and outcome measures will also align with the SRRR Trial Development Framework (Bernhardt et al., 2019) and be reported in accordance with the Template for Intervention Description and Replication (TIDieR) checklist (Gomes et al., 2023; Hoffmann et al., 2014).

10.4 Strengths and limitations of this program of research

10.4.1 Strengths

This program of research was developed to produce high quality research relevant to clinical practice. A systematic review with meta-analysis was completed to identify the optimal intervention to increase BDNF concentration post-stroke. The review was conducted in accordance with the PRISMA statement (Page et al., 2021) and incorporated the ROB 2 (Sterne et al., 2019) and ROBINS-I (Sterne et al., 2016) to assess the methodological quality of the studies included in the review (Boutron et al., 2022). The systematic review and meta-analysis was published in Stroke (Q1, impact factor of 10.17).

The mixed methods study design implemented in Study 2 (Chapter 6) incorporated questionnaires and interviews that were co-designed by lived experts to support alignment between researcher and consumer goals for this research project (Plant et al., 2016). People with stroke provided feedback on the content and wording of the questionnaire, as well as the accessibility of the questionnaire on REDCap. Health professionals provided feedback regarding the wording and duration of the questionnaire. The semi-structured interview was co-designed with a psychologist to ensure the use of open-ended questions, appropriate probing questions to obtain more information and assist with development of data analysis.

While the proposed RCT in this program of research was not completed due to Covid-19, rigour was ensured in the development of the study protocol. The RCT included blinded assessment to reduce the risk of bias during data collection (Higgins et al., 2022), followed the CONSORT statement (Maher et al., 2010) and intended to report the exercise intervention in accordance with the TiDIER guidelines (Gomes et al., 2023; Hoffmann et al., 2014). In addition, the historical control group included in this RCT included the same inclusion/exclusion criteria and completed the same mCIMT program as proposed in this study, ensuring comparison is possible (McNulty et al., 2015).

Additional strengths demonstrated within this program of research include; (a) the adaptation of the program of research during the Covid-19 pandemic, ensuring high quality and rigorous study design and data collection, (b) development of relationships between researchers and clinicians at potential recruitment sites to assist with the conduct of the RCT, (c) quick pivot of research questions and processes from in-person stroke participants to online platforms (Study 2) and healthy participants (Study 3), as well as (d) the recruitment and testing of 46 people with stroke, 45 health professionals and 31 healthy adults across Study 2, 3 and 4.

10.4.2 Limitations

The impact of Covid-19 on this program of research was significant and has been described earlier (Chapter 3).

Small sample sizes were recruited for Study 2, 3 and 4, which may limit the generalisability

of the results obtained. As outlined in Chapter 10.3.1, a more diverse sample of people with stroke and health professionals who work in stroke rehabilitation is needed to gain a deeper insight into the perspectives of HIIT after stroke. Culturally and linguistically diverse backgrounds, exercise affinities, impairment severity and health profession must be targeted. As outlined in Chapter 10.3.3, larger sample sizes are needed in Study 3 and 4 to identify changes in BDNF concentration and MAL-30 scores, respectively, to allow for a better indication of the relationship between the potential alternative measures proposed.

While co-design was implemented in this program of research (i.e., development of the questionnaires and interview scripts used in Study 2), lived experience was not sought in the early stages of the design and development of Study 5. Future studies should seek to involve lived experts at the idea development stage, ensuring this area of research is a topic of interest for the stroke community, and asking for consumer input across the timeline of the study (Boivin et al., 2018; Slattery et al., 2020).

In Study 3 and 4, while correlations may demonstrate a relationship between the variables, it must be noted that correlation does not equal agreement between the measures. The aim of these studies were to identify potential relationships between BDNF and lactate concentrations (i.e., Study 3) and the MAL-30 and REACH (i.e., Study 4). The results of these studies do not support the use of the alternative measure but do suggest further research is warranted.

10.5 Conclusions

This program of research concluded that high intensity aerobic exercise is needed to increase BDNF concentration after stroke. A program of high intensity aerobic exercise produces the largest increase in BDNF concentration; however, a single session is also sufficient to increase BDNF concentration. However, numerous barriers to the use of high intensity aerobic exercise, such as HIIT, restrict the participation in, and prescription of, such interventions in stroke rehabilitation. A lack of knowledge of the safety and benefits of HIIT are reported by people with stroke and health professionals working in stroke rehabilitation. Therefore, increased education targeting both people with stroke and health professionals

working in stroke rehabilitation is needed to facilitate greater use of HIIT in clinical practice. People with stroke also report a lack of support from health professionals and other people with stroke as a barrier to participation in HIIT. Access to allied health professionals specifically educated and trained in HIIT prescription may help to overcome this barrier, as well as increase the confidence of allied health professionals to prescribe HIIT to people with stroke. Both people with stroke and health professionals working in stroke rehabilitation also indicate framing the intervention around interval training, as opposed to 'high intensity' exercise may encourage greater uptake of HIIT.

The impact of HIIT on BDNF concentration and its role in facilitating improvements in motor skill acquisition and functional recovery after stroke requires further investigation. The benefits of a program of mCIMT after stroke are clearly demonstrated, however the effect of the addition of a HIIT program warrant further research. In addition, the investigation of the temporal ordering of HIIT and mCIMT may provide an opportunity to further explore the relationship between BDNF and lactate concentrations and the responsiveness of the REACH.

Chapter 11 REFERENCES

Abdullahi, A. (2018). Effects of number of repetitions and number of hours of shaping practice during constraint-induced movement therapy: A randomized controlled trial. *Neurology Research International*, *2018*, 5496408-5496409. https://doi.org/10.1155/2018/5496408

Abdullahi, A., Van Criekinge, T., Umar, N. A., Zakari, U. U., Truijen, S., & Saeys, W. (2020). Effect of constraint-induced movement therapy on persons-reported outcomes of health status after stroke: A systematic review and meta-analysis. *International Journal of Rehabilitation Research*, *44*(1), 15-23. https://doi.org/10.1097/MRR.0000000000000446

Adams, J. H. P., Bendixen, B. H., Kappelle, L. J., Biller, J., Love, B. B., Gordon, D. L., & Marsh, R. E. E. (1993) Classification of subtype of acute ischemic stroke: Definitions for use in a multicenter clinical trial: TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke, 24*(1), 35-41. https://doi.org/10.1161/01.STR.24.1.35

Aguiar, L. T., Nadeau, S., Teixeira-Salmela, L. F., Reis, M. T. F., Peniche, P. da C., & Faria, C. D. C. de M. (2022). Perspectives, satisfaction, self-efficacy, and barriers to aerobic exercise reported by individuals with chronic stroke in a developing country. *Disability and Rehabilitation*, *44*(13), 3089–3094. https://doi.org/10.1080/09638288.2020.1855260

Ahangar, A. A., Saadat, P., Heidari, B., Taheri, S. T., & Alijanpour, S. (2018). Sex difference in types and distribution of risk factors in ischemic and hemorrhagic stroke. *International Journal of Stroke*, *13*(1), 83-86. https://doi.org/10.1177/1747493017724626

Akoglu, H. (2018). User's guide to correlation coefficients. *Turkish Journal of Emergency Medicine*, *18*(3), 91–93. https://doi.org/10.1016/j.tjem.2018.08.001

Alcantara, C. C., García-Salazar, L. F., Silva-Couto, M. A., Santos, G. L., Reisman, D. S., & Russo, T. L. (2018). Post-stroke BDNF concentration changes following physical exercise: A systematic review. *Frontiers in Neurology*, *9*, 637-637. https://doi.org/10.3389/fneur.2018.00637

Alghamdi, I., Ariti, C., Williams, A., Wood, E., & Hewitt, J. (2021). Prevalence of fatigue after stroke: A systematic review and meta-analysis. *European Stroke Journal*, *6*(4), 319–332. https://doi.org/10.1177/23969873211047681

Algin, A., Erdogan, M. O., Aydin, I., Poyraz, M. K., & Sirik, M. (2019). Clinical usefulness of brain-derived neurotrophic factor and visinin-like protein-1 in early diagnostic tests for acute stroke. *American Journal of Emergency Medicine*, *37*(11), 2051-2054. https://doi.org/10.1016/j.ajem.2019.02.037

Alia, C., Spalletti, C., Lai, S., Panarese, A., Lamola, G., Bertolucci, F., Vallone, F., Di Garbo, A., Chisari, C., Micera, S., & Caleo, M. (2017). Neuroplastic changes following brain ischemia and their contribution to stroke recovery: Novel approaches in neurorehabilitation. *Frontiers in Cellular Neuroscience*, *11*, 76-76. https://doi.org/10.3389/fncel.2017.00076

Alomari, M. A., Khabour, O. F., Alawneh, K., Alzoubi, K. H., & Maikano, A. B. (2020). The importance of physical fitness for the relationship of BDNF with obesity measures in young normal-weight adults. *Heliyon*, *6*(3), e03490–. https://doi.org/10.1016/j.heliyon.2020.e03490

Amalia, L., & Dalimonthe, N. Z. (2020). Clinical significance of platelet-to-white blood cell ratio (PWR) and National Institute of Health stroke scale (NIHSS) in acute ischemic stroke. *Heliyon*, *6*(10), e05033-e05033. https://doi.org/10.1016/j.heliyon.2020.e05033

Amarenco, P. (2020). Transient Ischemic Attack. *New England Journal of Medicine*, *382*(20), 1933-1941. https://doi.org/10.1056/NEJMcp1908837

Anastasia, A., Deinhardt, K., Chao, M. V., Will, N. E., Irmady, K., Lee, F. S., Hempstead, B. L., & Bracken, C. (2013). Val66Met polymorphism of BDNF alters prodomain structure to induce neuronal growth cone retraction. *Nature Communications*, *4*(1), 2490-2490. https://doi.org/10.1038/ncomms3490

Andersson, N. (2017). Community-led trials: Intervention co-design in a cluster randomised controlled trial. *BMC Public Health*, *17*(Suppl 1), 397–397. https://doi.org/10.1186/s12889-017-4288-6

Andrabi, M., Taub, E., Mckay Bishop, S., Morris, D., & Uswatte, G. (2022). Acceptability of constraint induced movement therapy: influence of perceived difficulty and

expected treatment outcome. *Topics in Stroke Rehabilitation, 29*(7), 507–515. https://doi.org/10.1080/10749357.2021.1956046

Anjos, J. M., Neto, M. G., dos Santos, F. S., Almeida, K. de O., Bocchi, E. A., Lima Bitar, Y. de S., & Duraes, A. R. (2022). The impact of high-intensity interval training on functioning and health-related quality of life In post-stroke patients: A systematic review with meta-analysis. *Clinical Rehabilitation*, *36*(6), 726–739. https://doi.org/10.1177/02692155221087082

Antunes, B. M., Rossi, F. E., Teixeira, A. M., & Lira, F. S. (2020). Short-time high-intensity exercise increases peripheral BDNF in a physical fitness-dependent way in healthy men. *European Journal of Sport Science, 20*(1), 43–50. https://doi.org/10.1080/17461391.2019.1611929

Arazi, H., Babaei, P., Moghimi, M., & Asadi, A. (2021). Acute effects of strength and endurance exercise on serum BDNF and IGF-1 levels in older men. *BMC Geriatrics*, *21*(1), 50–50. https://doi.org/10.1186/s12877-020-01937-6

Askim, T., Dahl, A. E., Aamot, I. L., Hokstad, A., Helbostad, J., & Indredavik, B. (2014). High-intensity aerobic interval training for patients 3-9 months after stroke: A feasibility study. *Physiotherapy Research International: The Journal for Researchers and Clinicians in Physical Therapy*, *19*(3), 129-139. https://doi.org/10.1002/pri.1573

Atkinson, A. J., Colburn, W. A., DeGruttola, V. G., DeMets, D. L., Downing, G. J., Hoth, D. F., Oates, J. A., Peck, C. C., Schooley, R. T., Spilker, B. A., Woodcock, J., & Zeger, S. L. (2001). Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clinical Pharmacology and Therapeutics*, *69*(3), 89-95. https://doi.org/10.1067/mcp.2001.113989

Australian Catholic University. (2021). *COVID-19 research FAQs*. Available from https://www.acu.edu.au/research-and-enterprise/covid-19-faqs

Australian Physiotherapy Association. (2011). *Standards for physiotherapy practices*. Australian Physiotherapy Association. Retrieved 7 March from https://australian.physio/sites/default/files/tools/Resources_Private_Practice_Standards_for_physiotherapy_practices_2011.pdf

Baig, S., Moyle, B., Redgrave, J., Majid, A., & Ali, A. (2020). Exercise referral to promote cardiovascular health in stroke and TIA patients: a pilot feasibility study. *BMJ Open*

Sport & Exercise Medicine, 6(1), e000929–e000929. https://doi.org/10.1136/bmjsem-2020-000929

Bakheit, A. M., Zakine, B., Maisonobe, P., Aymard, C., Fhedoroff, K., Hefter, H., Jacinto, J., Jost, W. H., Molteni, F., Stam, H., Turner-Stokes, L., & Wissel, J. (2010). The profile of patients and current practice of treatment of upper limb muscle spasticity with botulinum toxin type A: An international survey. *International Journal of Rehabilitation Research*, *33*(3), 199-204. https://doi.org/10.1097/MRR.0b013e328332f5e0

Bakhti, K. K. A., Mottet, D., Schweighofer, N., Froger, J., & Laffont, I. (2017). Proximal arm non-use when reaching after a stroke. *Neuroscience Letters*, *657*, 91-96. https://doi.org/10.1016/j.neulet.2017.07.055

Baldwin, C. R., Harry, A. J., Power, L. J., Pope, K. L., & Harding, K. E. (2018). Modified constraint-induced movement therapy is a feasible and potentially useful addition to the community rehabilitation took kit after stroke: A pilot randomised control trial. *Australian Occupational Therapy Journal*, *65*(6), 503-511. https://doi.org/10.1111/1440-1630.12488

Balkaya, M., & Cho, S. (2019). Genetics of stroke recovery: BDNF val66met polymorphism in stroke recovery and its interaction with aging. *Neurobiology of Disease*, *126*, 36-46. https://doi.org/10.1016/j.nbd.2018.08.009

Ballester-Ferrer, J. A., Roldan, A., Cervelló, E., & Pastor, D. (2022). Memory modulation by exercise in young adults is related to lactate and not affected by sex or BDNF polymorphism. *Biology*, *11*(10), 1541-. https://doi.org/10.3390/biology11101541

Bamford, J. M., Sandercock, P. A., Warlow, C. P., & Slattery, J. (1989). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, *20*(6), 828-828. https://doi.org/10.1161/01.STR.20.6.828

Bang, O. Y. (2017). Advances in biomarker for stroke patients: From marker to regulator. *Precision and Future Medicine*, *1*(1), 32-42. https://doi.org/10.23838/pfm.2017.00052

Banks, G., Bernhardt, J., Churilov, L., & Cumming, T. B. (2012). Exercise preferences are different after stroke. *Stroke Research and Treatment*, *2012*, 890946–890949. https://doi.org/10.1155/2012/890946

Bayona, N. A., Bitensky, J., Salter, K., & Teasell, R. (2005). The Role of Task-Specific Training in Rehabilitation Therapies. *Topics in Stroke Rehabilitation*, *12*(3), 58–65. https://doi.org/10.1310/BQM5-6YGB-MVJ5-WVCR

Beckwée, D., Lefeber, N., Bautmans, I., Cuypers, L., De Keersmaecker, E., De Raedt, S., Kerckhofs, E., Nagels, G., Njemini, R., Perkisas, S., Scheys, E., & Swinnen, E. (2021). Muscle changes after stroke and their impact on recovery: Time for a paradigm shift? Review and commentary. *Topics in Stroke Rehabilitation*, *28*(2), 104-111. https://doi.org/10.1080/10749357.2020.1783916

Begliuomini, S., Casarosa, E., Pluchino, N., Lenzi, E., Centofanti, M., Freschi, L., Pieri, M., Genazzani, A. D., Luisi, S., & Genazzani, A. R. (2007). Influence of endogenous and exogenous sex hormones on plasma brain-derived neurotrophic factor. *Human Reproduction*, *22*(4), 995-1002. https://doi.org/10.1093/humrep/del479

Bembenek, J. P., Kurczych, K., Kłysz, B., Cudna, A., Antczak, J., & Członkowska, A. (2020). Prediction of recovery and outcome using motor evoked potentials and brain derived neurotrophic factor in subacute stroke. *Journal of Stroke and Cerebrovascular Diseases, 29*(11). https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105202

Berge, E., Stapf, C., Al-Shahi Salman, R., Ford, G. A., Sandercock, P., van der Worp, H. B., Petersson, J., Dippel, D. W., Krieger, D. W., & Lees, K. R. (2016). Methods to improve patient recruitment and retention in stroke trials. *International Journal of Stroke*, *11*(6), 663–676. https://doi.org/10.1177/1747493016641963

Bergersen, L. H. (2007). Is lactate food for neurons? Comparison of monocarboxylate transporter subtypes in brain and muscle. *Neuroscience, 145*(1), 11–19. https://doi.org/10.1016/j.neuroscience.2006.11.062

Bergersen, L. H. (2015). Lactate transport and signaling in the brain: Potential therapeutic targets and roles in body—brain interaction. *Journal of Cerebral Blood Flow & Metabolism, 35*(2), 176–185. https://doi.org/10.1038/jcbfm.2014.206

Bernhardt, J., Borschmann, K., Boyd, L., Carmichael, S. T., Corbett, D., Cramer, S. C., Hoffmann, T., Kwakkel, G., Savitz, S. I., Saposnik, G., Walker, M., & Ward, N. (2016). Moving rehabilitation research forward: Developing consensus statements for

rehabilitation and recovery research. *International Journal of Stroke*, *11*(4), 454-458. https://doi.org/10.1177/1747493016643851

Bernhardt, J., Hayward, K. S., Dancause, N., Lannin, N. A., Ward, N. S., Nudo, R. J., Farrin, A., Churilov, L., Boyd, L. A., Jones, T. A., Carmichael, S. T., Corbett, D., & Cramer, S. C. (2019). A stroke recovery trial development framework: Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable. *International Journal of Stroke, 14*(8), 792–802.

Bernhardt, J., Hayward, K. S., Kwakkel, G., Ward, N. S., Wolf, S. L., Borschmann, K., Krakauer, J. W., Boyd, L. A., Carmichael, S. T., Corbett, D., & Cramer, S. C. (2017). Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. *International Journal of Stroke*, *12*(5), 444-450. https://doi.org/10.1177/1747493017711816

Berretta, A., Tzeng, Y.-C., & Clarkson, A. N. (2014). Post-stroke recovery: The role of activity-dependent release of brain-derived neurotrophic factor. *Expert Review of Neurotherapeutics*, *14*(11), 1335-1344. https://doi.org/10.1586/14737175.2014.969242

Bhatnagar, K., Bever, C. T., Tian, J., Zhan, M., & Conroy, S. S. (2020). Comparing home upper extremity activity with clinical evaluations of arm function in chronic stroke. *Archives of Rehabilitation Research and Clinical Translation, 2*(2), 100048–. https://doi.org/10.1016/j.arrct.2020.100048

Billinger, S. A., Arena, R., Bernhardt, J., Eng, J. J., Franklin, B. A., Johnson, C. M., MacKay-Lyons, M., Macko, R. F., Mead, G. E., Roth, E. J., Shaughnessy, M., & Tang, A. (2014). Physical activity and exercise recommendations for stroke survivors: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, *45*(8), 2532-2553. https://doi.org/10.1161/STR.0000000000000022

Binder, D. K., & Scharfman, H. E. (2004). Brain-derived neurotrophic factor. *Growth Factors*, *22*(3), 123-131. https://doi.org/10.1080/08977190410001723308

Birchenall, J., Térémetz, M., Roca, P., Lamy, J.-C., Oppenheim, C., Maier, M. A., Mas, J.-L., Lamy, C., Baron, J.-C., & Lindberg, P. G. (2019). Individual recovery profiles of manual dexterity, and relation to corticospinal lesion load and excitability after stroke: A

longitudinal pilot study. *Neurophysiologie Clinique*, *49*(2), 149-164. https://doi.org/10.1016/j.neucli.2018.10.065

Bird, M., McGillion, M., Chambers, E. M., Dix, J., Fajardo, C. J., Gilmour, M., Levesque, K., Lim, A., Mierdel, S., Ouellette, C., Polanski, A. N., Reaume, S. V., Whitmore, C., & Carter, N. (2021). A generative co-design framework for healthcare innovation: development and application of an end-user engagement framework. *Research Involvement and Engagement*, *7*(1), 12–12. https://doi.org/10.1186/s40900-021-00252-7

Birt, L., Scott, S., Cavers, D., Campbell, C., & Walter, F. (2016). Member checking: A Tool to enhance trustworthiness or merely a nod to validation? *Qualitative Health Research, 26*(13), 1802–1811. https://doi.org/10.1177/1049732316654870

Bluestone, J., Johnson, P., Fullerton, J., Carr, C., Alderman, J., & BonTempo, J. (2013). Effective in-service training design and delivery: Evidence from an integrative literature review. *Human Resources for Health*, *11*(1), 51–51. https://doi.org/10.1186/1478-4491-11-51

Boehme, A. K., Esenwa, C., & Elkind, M. S. V. (2017). Stroke risk factors, genetics, and prevention. *Circulation Research*, *120*(3), 472-495. https://doi.org/10.1161/CIRCRESAHA.116.308398

Boivin, A., Richards, T., Forsythe, L., Grégoire, A., L'Espérance, A., Abelson, J., & Carman, K. L. (2018). Evaluating patient and public involvement in research. *BMJ (Online)*, *363*, k5147–k5147. https://doi.org/10.1136/bmj.k5147

Bonaventura, J. M., Sharpe, K., Knight, E., Fuller, K. L., Tanner, R. K., & Gore, C. J. (2015). Reliability and accuracy of six hand-held blood lactate analysers. *Journal of Sports Science & Medicine*, *14*(1), 203-214.

Bonner, N. S., O'Halloran, P. D., Bernhardt, J., & Cumming, T. B. (2016). Developing the stroke exercise preference inventory (SEPI). *PloS One, 11*(10), e0164120–e0164120. https://doi.org/10.1371/journal.pone.0164120

Booker, Q. S., Austin, J. D., & Balasubramanian, B. A. (2021). Survey strategies to increase participant response rates in primary care research studies. *Family Practice*, *38*(5), 699–702. https://doi.org/10.1093/fampra/cmab070

Borg, G. (1970). Perceived exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitation Medicine*, *2*(2), 92-98

Boutron, I., Page, M.J., Higgins, J.P.T., Altman, D.G., Lundh, A., & Hróbjartsson, A. (2022). Chapter 7: Considering bias and conflicts of interest among the included studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane. Available from www.training.cochrane.org/handbook.

Boyd, L. A., Hayward, K. S., Ward, N. S., Stinear, C. M., Rosso, C., Fisher, R. J., Carter, A. R., Leff, A. P., Copland, D. A., Carey, L. M., Cohen, L. G., Basso, D. M., Maguire, J. M., & Cramer, S. C. (2017). Biomarkers of stroke recovery: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *International Journal of Stroke*, *12*(5), 480–493. https://doi.org/10.1177/1747493017714176

Boyne, P., Billinger, S., MacKay-Lyons, M., Barney, B., Khoury, J., & Dunning, K. (2017). Aerobic exercise prescription in stroke rehabilitation: A web-based survey of US physical therapists. *Journal of Neurologic Physical Therapy*, *41*(2), 119–128. https://doi.org/10.1097/NPT.0000000000000177

Boyne, P., Billinger, S. A., Reisman, D. S., Awosika, O. O., Buckley, S., Burson, J., Carl, D., DeLange, M., Doren, S., Earnest, M., Gerson, M., Henry, M., Horning, A., Khoury, J. C., Kissela, B. M., Laughlin, A., McCartney, K., McQuaid, T., Miller, A., … Dunning, K. (2023). Optimal intensity and duration of walking rehabilitation in patients with chronic stroke: A randomized clinical trial. *JAMA Neurology*, *80*(4), 342–351. https://doi.org/10.1001/jamaneurol.2023.0033

Boyne, P., Meyrose, C., Westover, J., Whitesel, D., Hatter, K., Reisman, D. S., Cunningham, D., Carl, D., Jansen, C., Khoury, J.C., Gerson, M., Kissela, B., & Dunning, K. (2019). Exercise intensity affects acute neurotrophic and neurophysiological responses poststroke. *Journal of Applied Physiology (1985), 126*(2), 431–443. https://doi.org/10.1152/japplphysiol.00594.2018

Boyne, P., Meyrose, C., Westover, J., Whitesel, D., Hatter, K., Reisman, D. S., Carl, D., Khoury, J. C., Gerson, M., Kissela, B., & Dunning, K. (2020). Effects of exercise intensity on

acute circulating molecular responses post-stroke. *Neurorehabilitation and Neural Repair*, *34*(3), 222-234. https://doi.org/10.1177/1545968319899915

Brady, M. C., Ali, M., VandenBerg, K., Williams, L. J., Williams, L. R., Abo, M., Becker, F., Bowen, A., Brandenburg, C., Breitenstein, C., Bruehl, S., Copland, D. A., Cranfill, T. B., di Pietro-Bachmann, M., Enderby, P., Fillingham, J., Galli, F. L., Gandolfi, M., Glize, B., … Wright, H. H. (2020). Communicating simply, but not too simply: Reporting of participants and speech and language interventions for aphasia after stroke. *International Journal of Speech Language Pathology*, *22*(3), 302–312. https://doi.org/10.1080/17549507.2020.1762000

Brandt, N., Dethlefsen, M. M., Bangsbo, J., & Pilegaard, H. (2017). PGC-1α and exercise intensity dependent adaptations in mouse skeletal muscle. *PloS One, 12*(10), e0185993-e0185993. https://doi.org/10.1371/journal.pone.0185993

Braun, R. G., Kittner, S. J., Ryan, K. A., & Cole, J. W. (2020). Effects of the BDNF Val66Met polymorphism on functional status and disability in young stroke patients. *PloS One*, *15*(12), e0237033-e0237033. https://doi.org/10.1371/journal.pone.0237033

Brooks, G. A., Arevalo, J. A., Osmond, A. D., Leija, R. G., Curl, C. C., & Tovar, A. P. (2022). Lactate in contemporary biology: a phoenix risen. *The Journal of Physiology*, *600*(5), 1229–1251. https://doi.org/10.1113/JP280955

Brozek, J. L., Akl, E. A., Guyatt, G. H., Schünemann, H. J., Alonso-Coello, P., Lang, D., Jaeschke, R., Williams, J. W., Phillips, B., Lelgemann, M., Lethaby, A., & Bousquet, J. (2009). Grading quality of evidence and strength of recommendations in clinical practice guidelines Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy, 64*(5), 669–677. https://doi.org/10.1111/j.1398-9995.2009.01973.x

Bruno, D., & Schurmann Vignaga, S. (2019). Addenbrooke's cognitive examination III in the diagnosis of dementia: A critical review. *Neuropsychiatric Disease and Treatment*, *15*, 441-447. https://doi.org/10.2147/NDT.S151253

Buetefisch, C. M. (2015). Role of the contralesional hemisphere in post-stroke recovery of upper extremity motor function. *Frontiers in Neurology*, *6*, 214–214. https://doi.org/10.3389/fneur.2015.00214

Burns, P.B., Rohrich, R. J., & Chung, K. C. (2011). The levels of evidence and their role in evidence-based medicine. *Plastic and Reconstructive Surgery (1963)*, *128*(1), 305–310. https://doi.org/10.1097/PRS.0b013e318219c171

Calautti, C., Naccarato, M., Jones, P. S., Sharma, N., Day, D. D., Carpenter, A. T., Bullmore, E. T., Warburton, E. A., & Baron, J.-C. (2007). The relationship between motor deficit and hemisphere activation balance after stroke: A 3T fMRI study. *NeuroImage*, *34*(1), 322-331. https://doi.org/10.1016/j.neuroimage.2006.08.026

Calder, A., Sole, G., & Mulligan, H. (2022). Co-design of an educational resource with female partners of male stroke survivors to support physical activity participation. *International Journal of Environmental Research and Public Health*, *19*(24), 16856–. https://doi.org/10.3390/ijerph192416856

Camak, D. J. (2015). Addressing the burden of stroke caregivers: A literature review. *Journal of Clinical Nursing*, *24*(17), 2376-2382. https://doi.org/10.1111/jocn.12884

Canivet, A., Albinet, C. T., André, N., Pylouster, J., Rodríguez-Ballesteros, M., Kitzis, A., & Audiffren, M. (2015). Effects of BDNF polymorphism and physical activity on episodic memory in the elderly: A cross sectional study. *European Review of Aging and Physical Activity*, *12*(1), 15-15. https://doi.org/10.1186/s11556-015-0159-2

Canton-Martínez, E., Rentería, I., García-Suárez, P. C., Moncada-Jiménez, J., Machado-Parra, J. P., Lira, F. S., Johnson, D. K., & Jiménez-Maldonado, A. (2022). Concurrent training increases serum brain-derived neurotrophic factor in older adults regardless of the exercise frequency. *Frontiers in Aging Neuroscience, 14*. https://doi.org/10.3389/fnagi.2022.791698

Carcel, C., Harris, K., Peters, S. A. E., Sandset, E. C., Balicki, G., Bushnell, C. D., Howard, V. J., Reeves, M. J., Anderson, C. S., Kelly, P. J., & Woodward, M. (2021). Representation of women in stroke clinical trials a review of 281 trials involving more than 500,000 participants. *Neurology*, *97*(18), E1768–E1774. https://doi.org/10.1212/WNL.0000000000012767

Carcel, C., & Reeves, M. (2021). Under-enrollment of women in stroke clinical trials what are the causes and what should be done about it? *Stroke*, *52*(2), 452–457. https://doi.org/10.1161/STROKEAHA.120.033227

Carey, J. R., Kimberley, T. J., Lewis, S. M., Auerbach, E. J., Dorsey, L., Rundquist, P., & Ugurbil, K. (2002). Analysis of fMRI and finger tracking training in subjects with chronic stroke. *Brain*, *125*(4), 773–788. https://doi.org/10.1093/brain/awf091

Carey, L. M. (1995). Somatosensory loss after stroke. *Critical Reviews in Physical and Rehabilitative Medicine*, *7*(1), 51-91. https://doi.org/10.1615/CritRevPhysRehabilMed.v7.i1.40

Carlstedt, E., Månsson Lexell, E., Ståhl, A., Lindgren, A., & Iwarsson, S. (2022). Stroke survivors' preferences regarding study participation in rehabilitation research. BMC *Medical Research Methodology, 22*(1), 36–36. https://doi.org/10.1186/s12874-022-01521-z

Carmichael, S. T., Tatsukawa, K., Katsman, D., Tsuyuguchi, N., & Kornblum, H. I. (2004). Evolution of diaschisis in a focal stroke model. *Stroke*, *35*(3), 758-763. https://doi.org/10.1161/01.STR.0000117235.11156.55

Carrera, E., & Tononi, G. (2014). Diaschisis: past, present, future. *Brain*, *137*(Pt 9), 2408–2422. https://doi.org/10.1093/brain/awu101

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Reports*, *100*(2), 126-131.

Cassidy, J. M., & Cramer, S. C. (2017). Spontaneous and therapeutic-induced mechanisms of functional recovery after stroke. *Translational Stroke Research*, *8*(1), 33-46. https://doi.org/10.1007/s12975-016-0467-5

Chang, W. H., Shin, M. A., Lee, A., Kim, H., & Kim, Y.-H. (2018). Relationship between serum BDNF levels and depressive mood in subacute stroke patients: A preliminary study. *International Journal of Molecular Sciences*, *19*(10), 3131. https://doi.org/10.3390/ijms19103131

Charalambous, C. C., Alcantara, C. C., French, M. A., Li, X., Matt, K. S., Kim, H. E., Morton, S. M., & Reisman, D. S. (2018). A single exercise bout and locomotor learning after stroke: physiological, behavioural, and computational outcomes. *The Journal of Physiology*, *596*(10), 1999-2016. https://doi.org/10.1113/JP275881

Charalambous, C. C., Helm, E. E., Lau, K. A., Morton, S. M., & Reisman, D. S. (2018). The feasibility of an acute high-intensity exercise bout to promote locomotor learning

after stroke. *Topics in Stroke Rehabilitation*, *25*(2), 83–89. https://doi.org/10.1080/10749357.2017.1399527

Chaturvedi, P., Singh, A., Tiwari, V., & Thacker, A. (2020). Post-stroke BDNF concentration changes following proprioceptive neuromuscular facilitation (PNF) exercises. *Journal of Family Medicine and Primary Care*, *9*(7), 3361-3369. https://doi.org/10.4103/jfmpc.jfmpc_1051_19

Chen, P., Liu, T.-W., Tse, M. M. Y., Lai, C. K. Y., Tsoh, J., & Ng, S. S. M. (2022). The predictive role of hand section of fugl–meyer assessment and motor activity log in action research arm test in people with stroke. *Frontiers in Neurology*, *13*, 926130–926130. https://doi.org/10.3389/fneur.2022.926130

Chen, Z.-Y., Patel, P. D., Sant, G., Meng, C.-X., Teng, K. K., Hempstead, B. L., & Lee, F. S. (2004). Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *The Journal of Neuroscience*, *24*(18), 4401-4411. https://doi.org/10.1523/JNEUROSCI.0348-04.2004

Clarke, D. J., & Forster, A. (2015). Improving post-stroke recovery: the role of the multidisciplinary health care team. *Journal of Multidisciplinary Healthcare*, *8*, 433–442. https://doi.org/10.2147/JMDH.S68764

Coco, M., Caggia, S., Musumeci, G., Perciavalle, V., Graziano, A. C. E., Pannuzzo, G., & Cardile, V. (2013). Sodium L-lactate differently affects brain-derived neurothrophic factor, inducible nitric oxide synthase, and heat shock protein 70 kDa production in human astrocytes and SH-SY5Y cultures. *Journal of Neuroscience Research*, *91*(2), 313–320. https://doi.org/10.1002/jnr.23154

Cohen, L. G., & Dimyan, M. A. (2011). Neuroplasticity in the context of motor rehabilitation after stroke. *Nature Reviews. Neurology*, *7*(2), 76–85. https://doi.org/10.1038/nrneurol.2010.200

Condon, M., & Guidon, M. (2018). A survey of exercise professionals' barriers and facilitators to working with stroke survivors. *Health & Social Care in the Community*, *26*(2), 250-258. https://doi.org/10.1111/hsc.12517

Connell, L. A., Smith, M.-C., Byblow, W. D., & Stinear, C. M. (2018). Implementing biomarkers to predict motor recovery after stroke. *NeuroRehabilitation*, *43*(1), 41–50. https://doi.org/10.3233/NRE-172395

Cornish, A. K., Broadbent, S., & Cheema, B. S. (2011). Interval training for patients with coronary artery disease: A systematic review. *European Journal of Applied Physiology, 111*(4), 579–589. https://doi.org/10.1007/s00421-010-1682-5

Corraini, P., Szépligeti, S. K., Henderson, V. W., Ording, A. G., Horváth-Puhó, E., & Sørensen, H. T. (2018). Comorbidity and the increased mortality after hospitalization for stroke: a population-based cohort study. *Journal of Thrombosis and Haemostasis*, *16*(2), 242-252. https://doi.org/10.1111/jth.13908

Coxon, J. P., Cash, R. F. H., Hendrikse, J. J., Rogasch, N. C., Stavrinos, E., Suo, C., & Yücel, M. (2018). GABA concentration in sensorimotor cortex following high-intensity exercise and relationship to lactate levels. *The Journal of Physiology*, *596*(4), 691-702. https://doi.org/10.1113/JP274660

Craik, F. I. M., & Rose, N. S. (2012). Memory encoding and aging: A neurocognitive perspective. *Neuroscience and Biobehavioral Reviews*, *36*(7), 1729-1739. https://doi.org/10.1016/j.neubiorev.2011.11.007

Cramer, S. C., & Crafton, K. R. (2006). Somatotopy and movement representation sites following cortical stroke. *Experimental Brain Research*, *168*(1–2), 25–32. https://doi.org/10.1007/s00221-005-0082-2

Cramer, S. C., See, J., Liu, B., Edwardson, M., Wang, X., Radom-Aizik, S., Haddad, F., Shahbaba, B., Wolf, S. L., Dromerick, A. W., & Winstein, C. J. (2022). Genetic factors, brain atrophy, and response to rehabilitation therapy after stroke. *Neurorehabilitation and Neural Repair*, *36*(2), 131–139. https://doi.org/10.1177/15459683211062899

Cramer, S. C., Sur, M., Chen, W. G., Cohen, L. G., Decharms, C., Duffy, C. J., Eden, G. F., Fetz, E. E., Filart, R., Freund, M., Grant, S. J., Haber, S., Dobkin, B. H., Kalivas, P. W., Kolb, B., Kramer, A. F., Lynch, M., Mayberg, H. S., McQuillen, P. S., Nitkin, R., Pascual-Leone, A., Reuter-Lorenz, P., Schiff, N., O'Brien, C., Sharma, A., Shekim, L., Stryker, M., Sullivan, E. V., Vinogradov, S., Sanger, T. D., Trojanowski, J. Q., Rumsey, J. M., Hicks, R., Cameron, J., & Daofen, C. (2011). Harnessing neuroplasticity for clinical applications. *Brain*, *134*(Pt 6), 1591-1609. https://doi.org/10.1093/brain/awr039

Crofts, A., Kelly, M. E., & Gibson, C. L. (2020). Imaging functional recovery following ischemic stroke: Clinical and preclinical fMRI studies. *Journal of Neuroimaging*, *30*(1), 5–14. https://doi.org/10.1111/jon.12668

Crotty, N. M., Boland, M., Mahony, N., Donne, B., & Fleming, N. (2021). Reliability and validity of the Lactate Pro 2 Analyzer. *Measurement in Physical Education and Exercise Science*, *25*(3), 202-211. https://doi.org/10.1080/1091367X.2020.1865966

Crozier, J., Roig, M., Eng, J. J., MacKay-Lyons, M., Fung, J., Ploughman, M., Bailey, D. M., Sweet, S. N., Giacomantonio, N., Thiel, A., Trivino, M., & Tang, A. (2018). High-intensity interval training after stroke: An opportunity to promote functional recovery, cardiovascular health, and neuroplasticity. *Neurorehabilitation and Neural Repair*, *32*(6-7), 543-556. https://doi.org/10.1177/1545968318766663

Currie, J., Ramsbottom, R., Ludlow, H., Nevill, A., & Gilder, M. (2009). Cardio-respiratory fitness, habitual physical activity and serum brain derived neurotrophic factor (BDNF) in men and women. *Neuroscience Letters*, *451*(2), 152–155. https://doi.org/10.1016/j.neulet.2008.12.043

Cusick, A., Lannin, N., & Kinnear, B. Z. (2015). Upper limb spasticity management for patients who have received Botulinum Toxin A injection: Australian therapy practice. *Australian Occupational Therapy Journal*, *62*(1), 27-40. https://doi.org/10.1111/1440-1630.12142

Dahms, C., Brodoehl, S., Witte, O. W., & Klingner, C. M. (2020). The importance of different learning stages for motor sequence learning after stroke. *Human Brain Mapping, 41*(1), 270–286. https://doi.org/10.1002/hbm.24793

Dalton, E. J., Lannin, N. A., Campbell, B. C., Churilov, L., & Hayward, K. S. (2023). Enhancing generalizability of stroke clinical trial results: Illustrations from upper-limb motor recovery trials. *International Journal of Stroke, 18*(5), 532–542. https://doi.org/10.1177/17474930221135730

Damush, T. M., Plue, L., Bakas, T., Schmid, A., & Williams, L. S. (2007). Barriers and facilitators to exercise among stroke survivors. *Rehabilitation Nursing*, *32*(6), 253-262. https://doi.org/10.1002/j.2048-7940.2007.tb00183.x

Debarnot, U., Neveu, R., Samaha, Y., Saruco, E., Macintyre, T., & Guillot, A. (2019). Acquisition and consolidation of implicit motor learning with physical and mental practice across multiple days of anodal tDCS. *Neurobiology of Learning and Memory*, 164, 107062–107062. https://doi.org/10.1016/j.nlm.2019.107062

de Morais, V. A. C., Tourino, M. F. d. S., Almeida, A. C. d. S., Albuquerque, T. B. D., Linhares, R. C., Christo, P. P., Martinelli, P. M., & Scalzo, P. L. (2018). A single session of moderate intensity walking increases brain-derived neurotrophic factor (BDNF) in the chronic post-stroke patients. *Topics in Stroke Rehabilitation, 25*(1), 1-5. https://doi.org/10.1080/10749357.2017.1373500

De Silva, T. M., & Faraci, F. M. (2017). Hypertension. In L. R. Caplan, J. Biller, M. C. Leary, E. H. Lo, A. J. Thomas, M. Yenari, & J. H. Zhang (Eds.), *Primer on Cerebrovascular Diseases (Second Edition)* (pp. 153-157). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-803058-5.00031-X

De Vincenti, A. P., Ríos, A. S., Paratcha, G., & Ledda, F. (2019). Mechanisms that modulate and diversify BDNF functions: Implications for hippocampal synaptic plasticity. *Frontiers in Cellular Neuroscience*, *13*, 135-135. https://doi.org/10.3389/fncel.2019.00135

Débora Pacheco, B., Guimarães Caetano, L. C., Amorim Samora, G., Sant'Ana, R., Fuscaldi Teixeira-Salmela, L., & Scianni, A. A. (2021). Perceived barriers to exercise reported by individuals with stroke, who are able to walk in the community. *Disability and Rehabilitation*, 43(3), 331-337. https://doi.org/10.1080/09638288.2019.1624396

Deloitte Access Economics. (2020). No postcode untouched: Stroke in Australia 2020. Stroke Foundation. https://strokefoundation.org.au/-/media/8BF4E14FA71949EAAFB34C7F39FDCD25.ashx?la=en

Di Pino, G., Pellegrino, G., Capone, F., Assenza, G., Florio, L., Falato, E., Lotti, F., & Di Lazzaro, V. (2016). Val66Met BDNF polymorphism implies a different way to recover from stroke rather than a worse overall recoverability. *Neurorehabilitation and Neural Repair, 30*(1), 3-8. https://doi.org/10.1177/1545968315583721

Dillman, D. A., Smyth, J. D., & Christian, L. M. (2014). *Internet, phone, mail, and mixed-mode surveys: The tailored design method* (Fourth edition). Wiley.

Dinoff, A., Herrmann, N., Swardfager, W., Liu, C. S., Sherman, C., Chan, S., & Lanctôt, K. L. (2016). The effect of exercise training on resting concentrations of peripheral brain-derived neurotrophic factor (BDNF): A meta-analysis. *PloS One, 11*(9), e0163037. https://doi.org/10.1371/journal.pone.0163037

Dodd, K. C., Nair, V. A., & Prabhakaran, V. (2017). Role of the contralesional vs. ipsilesional hemisphere in stroke recovery. *Frontiers in Human Neuroscience*, *11*, 469–469. https://doi.org/10.3389/fnhum.2017.00469

Dos Santos, A., Balabanski, A. H., Katzenellenbogen, J. M., Thrift, A. G., Burchill, L., & Parsons, M. W. (2021). A narrative review of stroke incidence, risk factors and treatment in Indigenous Peoples of the world. *Vessel Plus, 5*(21), 1-16. https://doi.org/10.20517/2574-1209.2020.69

Doussoulin, A., Rivas, C., Rivas, R., & Saiz, J. (2018). Effects of modified constraint-induced movement therapy in the recovery of upper extremity function affected by a stroke: A single-blind randomized parallel trial-comparing group versus individual intervention. *International Journal of Rehabilitation Research*, *41*(1), 35-40. https://doi.org/10.1097/MRR.0000000000000257

Doyle, L., & MacKay-Lyons, M. (2013). Utilization of aerobic exercise in adult neurological rehabilitation by physical therapists in Canada. *Journal of Neurologic Physical Therapy*, *37*(1), 20–26. https://doi.org/10.1097/NPT.0b013e318282975c

Doyle, S. D., Bennett, S., & Dudgeon, B. (2014). Upper limb post-stroke sensory impairments: the survivor's experience. *Disability and Rehabilitation*, *36*(12), 993-1000. https://doi.org/10.3109/09638288.2013.825649

Drigny, J., Joussain, C., Gremeaux, V., Morello, R., Van Truc, P. H., Stapley, P., Touzé, E., & Ruet, A. (2019). Development and validation of a questionnaire to assess barriers to physical activity after stroke: The Barriers to physical activity after stroke scale. *Archives of Physical Medicine and Rehabilitation*, *100*(9), 1672–1679. https://doi.org/10.1016/j.apmr.2018.12.034

Dromerick, A. W., Lang, C. E., Birkenmeier, R. L., Wagner, J. M., Miller, J. P., Videen, T. O., Powers, W. J., Wolf, S. L., & Edwards, D. F. (2009). Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): A single-center RCT. *Neurology, 73(*3), 195–201. https://doi.org/10.1212/WNL.0b013e3181ab2b27

Du, X., Chen, W., Zhang, N., Bian, X., & Yu, W. (2021). The effects of low-intensity resistance training with or without blood flow restriction on serum BDNF, VGEF and perception in patients with post-stroke depression. *Neuroendocrinology Letter, 42*(4), 229-235.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., & Weinberger, D. R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*(2), 257-269. https://doi.org/10.1016/S0092-8674(03)00035-7

El-Tamawy, M. S., Abd-Allah, F., Ahmed, S. M., Darwish, M. H., & Khalifa, H. A. (2014). Aerobic exercises enhance cognitive functions and brain derived neurotrophic factor in ischemic stroke patients. *NeuroRehabilitation*, *34*(1), 209-213. https://doi.org/10.3233/NRE-131020

El Hayek, L., Khalifeh, M., Zibara, V., Abi Assaad, R., Emmanuel, N., Karnib, N., El-Ghandour, R., Nasrallah, P., Bilen, M., Ibrahim, P., Younes, J., Abou Haidar, E., Barmo, N., Jabre, V., Stephan, J. S., & Sleiman, S. F. (2019). Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). *The Journal of Neuroscience*, *39*(13), 2369-2382. https://doi.org/10.1523/JNEUROSCI.1661-18.2019

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Heo, S., McLaren, M., Pence, B. D., Martin, S. A., Vieira, V. J., Woods, J. A., McAuley, E., & Kramer, A. F. (2010). Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. *The Journal of Neuroscience*, *30*(15), 5368–5375. https://doi.org/10.1523/JNEUROSCI.6251-09.2010

Espernberger, K. R., Fini, N. A., & Peiris, C. L. (2021). Personal and social factors that influence physical activity levels in community-dwelling stroke survivors: A systematic review of qualitative literature. *Clinical Rehabilitation*, *35*(7), 1044-1055. https://doi.org/10.1177/0269215521993690

Exercise and Sport Science Australia. (2015). *Accredited exercise physiologist professional standards*. Exercise and Sport Science Australia. Retrieved 7 March 2023 from https://www.essa.org.au/wp-content/uploads/2016/12/AEP-Professional-Standards-with-coverpage_approved.pdf

Exercise and Sport Science Australia. (2019). Adult pre-exercise screening system (APSS) screening tool. Retrieved 23 April 2023 from https://www.essa.org.au/Public/ABOUT_ESSA/Pre-Exercise_Screening_Systems.aspx

Fernández-Rodríguez, R., Álvarez-Bueno, C., Martínez-Ortega, I. A., Martínez-Vizcaíno, V., Mesas, A. E., & Notario-Pacheco, B. (2021). Immediate effect of high-intensity exercise on brain-derived neurotrophic factor in healthy young adults: A systematic review and meta-analysis. *Journal of Sport and Health Science, 11*(3), 367-375. https://doi.org/10.1016/j.jshs.2021.08.004

Ferris, L. T., Williams, J. S., & Shen, C.-L. (2007). The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Medicine and Science in Sports and Exercise*, *39*(4), 728–734. https://doi.org/10.1249/mss.0b013e31802f04c7

Fini, N. A., Bernhardt, J., Churilov, L., Clark, R., & Holland, A. E. (2021). Adherence to physical activity and cardiovascular recommendations during the 2 years after stroke rehabilitation discharge. *Annals of Physical and Rehabilitation Medicine*, *64*(2), 101455. https://doi.org/10.1016/j.rehab.2020.03.018

Fini, N. A., Bernhardt, J., Said, C. M., & Billinger, S. A. (2021). How to address physical activity participation after stroke in research and clinical practice. *Stroke*, *52*(6), e274-e277. https://doi.org/10.1161/STROKEAHA.121.034557

Fini, N. A., Holland, A. E., Keating, J., Simek, J., & Bernhardt, J. (2017). How physically active are people following stroke? Systematic review and quantitative synthesis. *Physical Therapy*, *97*(7), 707-717. https://doi.org/10.1093/ptj/pzx038

Fleet, A., Page, S. J., MacKay-Lyons, M., & Boe, S. G. (2014). Modified constraint-induced movement therapy for upper extremity recovery post stroke: What is the evidence? *Topics in Stroke Rehabilitation*, *21*(4), 319-331. https://doi.org/10.1310/tsr2104-319

Fan, W., & Yan, Z. (2010). Factors affecting response rates of the web survey: A systematic review. *Computers in Human Behavior, 26*(2), 132–139. https://doi.org/10.1016/j.chb.2009.10.015

French, M. A., Morton, S. M., Pohlig, R. T., & Reisman, D. S. (2018). The relationship between BDNF Val66Met polymorphism and functional mobility in chronic stroke survivors. *Topics in Stroke Rehabilitation, 25*(4), 276-280. https://doi.org/10.1080/10749357.2018.1437938

Fugl-Meyer, A. R., Jääskö, L., Leyman, I., Olsson, S., & Steglind, S. (1975). The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scandinavian Journal of Rehabilitation Medicine*, *7*(1), 13-31.

Gagliardi, A. R., Berta, W., Kothari, A., Boyko, J., & Urquhart, R. (2016). Integrated knowledge translation (IKT) in health care: A scoping review. *Implementation Science*, *11*(38), 38–38. https://doi.org/10.1186/s13012-016-0399-1

Gale, N. K., Heath, G., Cameron, E., Rashid, S., & Redwood, S. (2013). Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology, 13*(1), 117–117. https://doi.org/10.1186/1471-2288-13-117

Gallanagh, S., Quinn, T. J., Alexander, J., & Walters, M. R. (2011). Physical activity in the prevention and treatment of stroke. *ISRN Neurology*, *2011*, 953818-953810. https://doi.org/10.5402/2011/953818

García-Suárez, P. C., Rentería, I., Moncada-Jiménez, J., Fry, A. C., & Jiménez-Maldonado, A. (2020). Acute systemic response of BDNF, lactate and cortisol to strenuous exercise modalities in healthy untrained women. *Dose-Response*, *18*(4), 1559325820970818-1559325820970818. https://doi.org/10.1177/1559325820970818

Gaskins, N. J., Bray, E., Hill, J. E., Doherty, P. J., Harrison, A., & Connell, L. A. (2019). Factors influencing implementation of aerobic exercise after stroke: A systematic review. *Disability and Rehabilitation*, 1-15. https://doi.org/10.1080/09638288.2019.1704075

Gejl, A. K., Enevold, C., Bugge, A., Andersen, M. S., Nielsen, C. H., & Andersen, L. B. (2019). Associations between serum and plasma brain-derived neurotrophic factor and influence of storage time and centrifugation strategy. *Scientific Reports*, *9*(1), 9655-9659. https://doi.org/10.1038/s41598-019-45976-5

Gibala, M. J., Little, J. P., MacDonald, M. J., & Hawley, J. A. (2012). Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal of Physiology*, *590*(5), 1077-1084. https://doi.org/10.1113/jphysiol.2011.224725

Gjellesvik, T. I., Becker, F., Tjønna, A. E., Indredavik, B., Lundgaard, E., Solbakken, H., Brurok, B., Tørhaug, T., Lydersen, S., & Askim, T. (2021). Effects of high-intensity interval training after stroke (the HIIT stroke study) on physical and cognitive function: A multicenter randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, *102*(9), 1683-1691. https://doi.org/10.1016/j.apmr.2021.05.008

Gjellesvik, T. T., Brurok, B., Hoff, J., Tørhaug, T., & Helgerud, J. (2012). Effect of high aerobic intensity interval treadmill walking in people with chronic stroke: A pilot study with

one year follow-up. *Topics in Stroke Rehabilitation*, *19*(4), 353-360. https://doi.org/10.1310/tsr1904-353

Gladden, L. B. (2004). Lactate metabolism: A new paradigm for the third millennium. *The Journal of Physiology, 558*(1), 5–30. https://doi.org/10.1113/jphysiol.2003.058701

Gladstone, D.J., Danells, C. J., & Black, S. E. (2002). The Fugl-Meyer Assessment of motor recovery after stroke: a critical review of its measurement properties. *Neurorehabilitation and Neural Repair*, *16*(3), 232–240. https://doi.org/10.1177/154596802401105171

Gomes, E. M., Alder, G., Oslen, S., & Signal, N. (2023, August 22-25). *The TIDieR-Rehab Checklist: Enhancing the reporting quality of rehabilitation interventions and dosage parameters through an extension of the Template for Intervention Description and Replication (TIDieR).* The Combined Stroke Society of Australasia and Smart Strokes Nursing and Allied Health Scientific Meeting, Melbourne, VIC, Australia. https://doi.org/10.1177/17474930231188838

Gonzalez, A., Gaines, M., Gallegos, L. Y., Guevara, R., & Gomez, F. A. (2018). Thread- paper, and fabric enzyme-linked immunosorbent assays (ELISA). *Methods, 146*, 58-65. https://doi.org/10.1016/j.ymeth.2018.02.008

Gray, V., Rice, C. L., & Garland, S. J. (2012). Factors that influence muscle weakness following stroke and their clinical implications: A critical review. *Physiotherapy Canada*, *64*(4), 415-426. https://doi.org/10.3138/ptc.2011-03

Grefkes, C., & Fink, G. R. (2020). Recovery from stroke: Current concepts and future perspectives. *Neurological Research and Practice*, *2*(1), 17-17. https://doi.org/10.1186/s42466-020-00060-6

Grefkes, C., & Ward, N. S. (2014). Cortical reorganization after stroke: How much and how functional? *The Neuroscientist*, *20*(1), 56–70. https://doi.org/10.1177/1073858413491147

Grindell, C., Coates, E., Croot, L., & O'Cathain, A. (2022). The use of co-production, co-design and co-creation to mobilise knowledge in the management of health conditions: A systematic review. *BMC Health Services Research*, *22*(1), 877–877. https://doi.org/10.1186/s12913-022-08079-y

Griffin, É. W., Mullally, S., Foley, C., Warmington, S. A., O'Mara, S. M., & Kelly, Á. M. (2011). Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiology & Behavior*, *104*(5), 934-941. https://doi.org/10.1016/j.physbeh.2011.06.005

Grysiewicz, R. A., Thomas, K., & Pandey, D. K. (2008). Epidemiology of ischemic and hemorrhagic stroke: Incidence, prevalence, mortality, and risk factors. *Neurologic Clinics*, *26*(4), 871-895. https://doi.org/10.1016/j.ncl.2008.07.003

Gular, K., Sivasubramanian, V., Reddy, R. S., Tedla, J. S., & Dixit, S. (2022). The Mediating effect of age, gender, and post-stroke duration on the association between trunk and upper limb recovery in subacute stroke population: A cross-sectional study with mediation analysis. *International Journal of Environmental Research and Public Health*, *19*(23), 15644–. https://doi.org/10.3390/ijerph192315644

Gunnes, M., Langhammer, B., Aamot, I.-L., Lydersen, S., Ihle-Hansen, H., Indredavik, B., Reneflot, K. H., Schroeter, W., & Askim, T. (2019). Adherence to a long-term physical activity and exercise program after stroke applied in a randomized controlled trial. *Physical Therapy*, *99*(1), 74-85. https://doi.org/10.1093/ptj/pzy126

Guzik, A., & Bushnell, C. (2017). Stroke epidemiology and risk factor management. *Cerebrovascular Disease*, *23*(1), 15-39. https://doi.org/10.1212/CON.0000000000000416

Haaland, K. Y., Mutha, P. K., Rinehart, J. K., Daniels, M., Cushnyr, B., & Adair, J. C. (2012). Relationship between arm usage and instrumental activities of daily living after unilateral stroke. *Archives of Physical Medicine and Rehabilitation*, *93*(11), 1957–1962. https://doi.org/10.1016/j.apmr.2012.05.011

Hall, J., Morton, S., Fitzsimons, C. F., Hall, J. F., Corepal, R., English, C., Forster, A., Lawton, R., Patel, A., Mead, G., & Clarke, D. J. (2020). Factors influencing sedentary behaviours after stroke: findings from qualitative observations and interviews with stroke survivors and their caregivers. *BMC Public Health, 20*(1), 967–967. https://doi.org/10.1186/s12889-020-09113-6

Hammer, A. M., & Lindmark, B. (2010). Responsiveness and validity of the motor activity log in patients during the subacute phase after stroke. *Disability and Rehabilitation, 32*(14), 1184–1193. https://doi.org/10.3109/09638280903437253

Han, P., Zhang, W., Kang, L., Ma, Y., Fu, L., Jia, L., Yu, H., Chen, X., Hou, L., Wang, L., Yu, X., Kohzuki, M., & Guo, Q. (2017). Clinical evidence of exercise benefits for stroke. In J. Xiao (Ed.), *Exercise for cardiovascular disease prevention and treatment: From molecular to clinical, part 2* (pp. 131-151). Springer Singapore. https://doi.org/10.1007/978-981-10-4304-8_9

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., & Weinberger, D. R. (2003). Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *The Journal of Neuroscience, 23*(17), 6690-6694. https://doi.org/10.1523/jneurosci.23-17-06690.2003

Harnish, S. M., Rodriguez, A. D., Blackett, D. S., Gregory, C., Seeds, L., Boatright, J. H., & Crosson, B. (2018). Aerobic exercise as an adjuvant to aphasia therapy: Theory, preliminary findings, and future directions. *Clinical Therapeutics*, *40*(1), 35-48.e36. https://doi.org/10.1016/j.clinthera.2017.12.002

Harper, L., Kalfa, N., Beckers, G. M. A., Kaefer, M., Nieuwhof-Leppink, A. J., Fossum, M., Herbst, K. W., & Bagli, D. (2020). The impact of COVID-19 on research. *Journal of Pediatric Urology, 16*(5), 715–716. https://doi.org/10.1016/j.jpurol.2020.07.002

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap): A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377-381. https://doi.org/10.1016/j.jbi.2008.08.010

Harrison, S., Henderson, J., Alderdice, F., & Quigley, M. A. (2019). Methods to increase response rates to a population-based maternity survey: A comparison of two pilot studies. *BMC Medical Research Methodology, 19*(1), 65–65. https://doi.org/10.1186/s12874-019-0702-3

Hatem, S. M., Saussez, G., Della Faille, M., Prist, V., Zhang, X., Dispa, D., & Bleyenheuft, Y. (2016). Rehabilitation of motor function after stroke: A multiple systematic review focused on techniques to stimulate upper extremity recovery. *Frontiers in Human Neuroscience*, *10*, 442-442. https://doi.org/10.3389/fnhum.2016.00442

Helm, E. E., Matt, K. S., Kirschner, K. F., Pohlig, R. T., Kohl, D., & Reisman, D. S. (2017). The influence of high intensity exercise and the Val66Met polymorphism on circulating

BDNF and locomotor learning. *Neurobiology of Learning and Memory*, *144*, 77-85. https://doi.org/10.1016/j.nlm.2017.06.003

Helm, E. E., Tyrell, C. M., Pohlig, R. T., Brady, L. D., & Reisman, D. S. (2016). The presence of a single-nucleotide polymorphism in the BDNF gene affects the rate of locomotor adaptation after stroke. *Experimental Brain Research*, *234*(2), 341-351. https://doi.org/10.1007/s00221-015-4465-8

Hennink, M. M., Kaiser, B. N., & Marconi, V. C. (2017). Code saturation versus meaning saturation: How many interviews are enough? *Qualitative Health Research*, *27*(4), 591–608. https://doi.org/10.1177/1049732316665344

Hermansen, L., & Stensvold, I. (1972). Production and removal of lactate during exercise in man. *Acta Physiologica Scandinavica*, *86*(2), 191-201. https://doi.org/10.1111/j.1748-1716.1972.tb05325.x

Herrera-Lopez, G., & Galvan, E. J. (2018). Modulation of hippocampal excitability via the hydroxycarboxylic acid receptor 1. *Hippocampus*, *28*(8), 557-567. https://doi.org/10.1002/hipo.22958

Higgins, J.P.T., Savović, J., Page, M.J., Elbers, R.G., Sterne, J.A.C. (2022). Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A. (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane. Available from https://training.cochrane.org/handbook.

Hikosaka, O., Nakamura, K., Sakai, K., & Nakahara, H. (2002). Central mechanisms of motor skill learning. *Current Opinion in Neurobiology, 12*(2), 217–222. https://doi.org/10.1016/S0959-4388(02)00307-0

Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D. G., Barbour, V., Macdonald, H., Johnston, M., Lamb, S. E., Dixon-Woods, M., McCulloch, P., Wyatt, J. C., Chan, A.-W., & Michie, S. (2014). Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ (Online)*, *348*. https://doi.org/10.1136/bmj.g1687

Hopkins, M. E., Davis, F. C., VanTieghem, M. R., Whalen, P. J., & Bucci, D. J. (2012). Differential effects of acute and regular physical exercise on cognition and affect. *Neuroscience*, *215*, 59-68. https://doi.org/10.1016/j.neuroscience.2012.04.056

Hornby, T. G., Rafferty, M. R., Pinto, D., French, D., & Jordan, N. (2022). Cost-effectiveness of high-intensity training vs conventional therapy for individuals with subacute stroke. *Archives of Physical Medicine and Rehabilitation*, *103*(7), S197–S204. https://doi.org/10.1016/j.apmr.2021.05.017

Hsieh, Y.-W., Wu, C.-Y., Lin, K.-C., Chang, Y.-F., Chen, C.-L., & Liu, J.-S. (2009). Responsiveness and validity of three outcome measures of motor function after stroke rehabilitation. *Stroke*, *40*(4), 1386-1391. https://doi.org/10.1161/STROKEAHA.108.530584

Hsu, C.-C., Fu, T.-C., Huang, S.-C., Chen, C. P.-C., & Wang, J.-S. (2020). Increased serum brain-derived neurotrophic factor with high-intensity interval training in stroke patients: A randomized controlled trial. *Annals of Physical and Rehabilitation Medicine*, *64*(4), 1-8. https://doi.org/https://doi.org/10.1016/j.rehab.2020.03.010

Hu, J., Cai, M., Shang, Q., Li, Z., Feng, Y., Liu, B., Xue, X., & Lou, S. (2021). Elevated lactate by high-intensity interval training regulates the hippocampal BDNF expression and the mitochondrial quality control system. *Frontiers in Physiology*, *12*, 629914-629914. https://doi.org/10.3389/fphys.2021.629914

Huangl, E. J., & Reichardt, L. F. (2001). Neurotrophins : Roles in neuronal development and function. *Annual Review of Neuroscience*, *24*(1), 677-736. https://doi.org/10.1146/annurev.neuro.24.1.677

Hunnicutt, J. L., & Gregory, C. M. (2017). Skeletal muscle changes following stroke: A systematic review and comparison to healthy individuals. *Topics in Stroke Rehabilitation*, *24*(6), 463-471. https://doi.org/10.1080/10749357.2017.1292720

Hussain, N., Sunnerhagen, K. S., & Alt Murphy, M. (2021). Recovery of arm function during acute to chronic stage of stroke quantified by kinematics. *Journal of Rehabilitation Medicine*, *53*(3), jrm00171-jrm00171. https://doi.org/10.2340/16501977-2813

Ibrahim, A. M., Chauhan, L., Bhardwaj, A., Sharma, A., Fayaz, F., Kumar, B., Alhashmi, M., AlHajri, N., Alam, M. S., & Pottoo, F. H. (2022). Brain-derived neurotropic factor in neurodegenerative disorders. *Biomedicines*, *10*(5), 1143-. https://doi.org/10.3390/biomedicines10051143

Ide, K., Schmalbruch, I. K., Quistorff, B., Horn, A., & Secher, N. H. (2000). Lactate, glucose and O2 uptake in human brain during recovery from maximal exercise. *The Journal of Physiology, 522*(1), 159–164. https://doi.org/10.1111/j.1469-7793.2000.t01-2-00159.xm

Inness, E. L., Jagroop, D., Andreoli, A., Bayley, M., Biasin, L., Danells, C., Hall, J., Mansfield, A., McDonald, A., Nishri, D., Salbach, N. M., Taylor, D., Wong, K., & Tang, A. (2022). Factors that influence the clinical implementation of aerobic exercise in stroke rehabilitation: A theory-informed qualitative study. *Physical Therapy, 102*(6), 1–. https://doi.org/10.1093/ptj/pzac014

Ioannidis, J.P.A. (2016). Why most clinical research is not useful. *PLoS Medicine*, *13*(6), e1002049–e1002049. https://doi.org/10.1371/journal.pmed.1002049

Jagosh, J., Macaulay, A. C., Pluye, P., Salsberg, J., Bush, P. L., Henderson, J., Sirett, E., Wong, G., Cargo, M., Herbert, C. P., Seifer, S. D., Green, L. W., & Greenhalgh, T. (2012). Uncovering the Benefits of Participatory Research: Implications of a Realist Review for Health Research and Practice. *The Milbank Quarterly*, *90*(2), 311–346. https://doi.org/10.1111/j.1468-0009.2012.00665.x

Jiménez-Maldonado, A., Rentería, I., García-Suárez, P. C., Moncada-Jiménez, J., & Freire-Royes, L. F. (2018). The impact of high-intensity interval training on brain derived neurotrophic factor in brain: A mini-review. *Frontiers in Neuroscience, 12,* 839-839. https://doi.org/10.3389/fnins.2018.00839

Johansen-Berg, H., Matthew F.S. Rushworth, Bogdanovic, M. D., Kischka, U., Wimalaratna, S., & Matthews, P. M. (2002). The role of ipsilateral premotor cortex in hand movement after stroke. *Proceedings of the National Academy of Sciences*, *99*(22), 14518–14523. https://doi.org/10.1073/pnas.222536799

Johansen-Berg, H. (2007). Functional imaging of stroke recovery: What have we learnt and where do we go from here? *International Journal of Stroke*, *2*(1), 7-16. https://doi.org/10.1111/j.1747-4949.2007.00093.x

Kambestad, O. B., Sirevåg, K., Mrdalj, J., Hovland, A., Endal, T. B., Andersson, E., Sjøbø, T. V., & Stavestrand, S. H. (2023). Physical exercise and serum bdnf-levels: accounting for the val66met polymorphism in older adults. *IBRO Neuroscience Reports*, *15*, S374–S375. https://doi.org/10.1016/j.ibneur.2023.08.709

Katan, M., & Luft, A. (2018). Global burden of stroke. *Seminars in Neurology*, *38*(02), 208-211. https://doi.org/10.1055/s-0038-1649503

Kelly, L. P., Devasahayam, A. J., Chaves, A. R., Wallack, E. M., McCarthy, J., Basset, F. A., & Ploughman, M. (2017). Intensifying functional task practice to meet aerobic training

guidelines in stroke survivors. *Frontiers in Physiology, 8*, 809-809. https://doi.org/10.3389/fphys.2017.00809

Kelly, K. M., Borstad, A. L., Kline, D., & Gauthier, L. V. (2018). Improved quality of life following constraint-induced movement therapy is associated with gains in arm use, but not motor improvement. *Topics in Stroke Rehabilitation*, *25*(7), 467-474. https://doi.org/10.1080/10749357.2018.1481605

Kim, B., & Winstein, C. (2017). Can neurological biomarkers of brain impairment be used to predict poststroke motor recovery? A systematic review. *Neurorehabilitation and Neural Repair*, *31*(1), 3-24. https://doi.org/10.1177/1545968316662708

Kim, Y., Lim, S. H., & Park, G.-Y. (2019). Crossed cerebellar diaschisis has an adverse effect on functional outcome in the subacute rehabilitation phase of stroke: A case-control study. *Archives of Physical Medicine and Rehabilitation*, *100*(7), 1308–1316. https://doi.org/10.1016/j.apmr.2019.01.026

Kim, E. J., Park, C. H., Chang, W. H., Lee, A., Kim, S. T., Shin, Y. I., & Kim, Y. H. (2016). The brain-derived neurotrophic factor Val66Met polymorphism and degeneration of the corticospinal tract after stroke: A diffusion tensor imaging study. *European Journal of Neurology*, *23*(1), 76-84. https://doi.org/10.1111/ene.12791

Kim, D. Y., Quinlan, E. B., Gramer, R., & Cramer, S. C. (2016b). BDNF Val66Met polymorphism is related to motor system function after stroke. *Physical Therapy, 96*(4), 533-539. https://doi.org/10.2522/ptj.2015-135

Kim, T. G., Bae, S. H., & Kim, K. Y. (2019). Effects of dual-task training with different intensity of aerobic exercise on cognitive function and neurotrophic factors in chronic stroke patients. *Research Journal of Pharmacy and Technology*, *12*(2), 693-698. https://doi.org/10.5958/0974-360X.2019.00123.9

Kim, Y. D., Cha, M.-J., Kim, J., Lee, D. H., Lee, H. S., Nam, C. M., Nam, H. S., & Heo, J. H. (2015). Long-term mortality in patients with coexisting potential causes of ischemic stroke. *International Journal of Stroke*, *10*(4), 541-546. https://doi.org/10.1111/ijs.12013

King, M., Kelly, L. P., Wallack, E. M., Hasan, S. M. M., Kirkland, M. C., Curtis, M. E., Chatterjee, T., McCarthy, J., & Ploughman, M. (2019). Serum levels of insulin-like growth factor-1 and brain-derived neurotrophic factor as potential recovery

biomarkers in stroke. *Neurological Research*, *41*(4), 354-363. https://doi.org/10.1080/01616412.2018.1564451

Kiper, P. P., Szczudlik, A. P., Venneri, A. P., Stozek, J. P., Luque-Moreno, C. P., Opara, J. P., Baba, A. M., Agostini, M. M., & Turolla, A. M. (2016). Computational models and motor learning paradigms: Could they provide insights for neuroplasticity after stroke? An overview. *Journal of the Neurological Sciences*, *369*, 141-148. https://doi.org/10.1016/j.jns.2016.08.019

Kleindorfer, D. O., Towfighi, A., Chaturvedi, S., Cockroft, K. M., Gutierrez, J., Lombardi-Hill, D., Kamel, H., Kernan, W. N., Kittner, S. J., Leira, E. C., Lennon, O., Meschia, J. F., Nguyen, T. N., Pollak, P. M., Santangeli, P., Sharrief, A. Z., Smith, S. C., Turan, T. N., & Williams, L. S. (2021). 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the American Heart Association/American Stroke Association. *Stroke*, *52*(7), E364–E467. https://doi.org/10.1161/STR.0000000000000375

Knaepen, K., Goekint, M., Heyman, E. M., & Meeusen, R. (2010). Neuroplasticity - Exercise-induced response of peripheral brain-derived neurotrophic factor: A systematic review of experimental studies in human subjects. *Sports Medicine*, *40*(9), 765-801. https://doi.org/10.2165/11534530-000000000-00000

Kong, K.-H., Chua, K. S. G., & Lee, J. (2011). Recovery of upper limb dexterity in patients more than 1 year after stroke: Frequency, clinical correlates and predictors. *NeuroRehabilitation*, *28*(2), 105-111. https://doi.org/10.3233/NRE-2011-0639

Koroleva, E. S., Tolmachev, I. V., Alifirova, V. M., Boiko, A. S., Levchuk, L. A., Loonen, A. J. M., & Ivanova, S. A. (2020). Serum BDNF's role as a biomarker for motor training in the context of AR-based rehabilitation after ischemic stroke. *Brain Sciences*, *10*(9), 623. https://doi.org/10.3390/brainsci10090623

Koton, S., Schneider, A. L. C., Rosamond, W. D., Shahar, E., Sang, Y., Gottesman, R. F., & Coresh, J. (2014). Stroke Incidence and Mortality Trends in US Communities, 1987 to 2011. *JAMA: The journal of the American Medical Association*, *312*(3), 259-268. https://doi.org/10.1001/jama.2014.7692

Kramer, S. F., Hung, S. H., & Brodtmann, A. (2019). The impact of physical activity before and after stroke on stroke risk and recovery: A narrative review. *Current Neurology and Neuroscience Reports*, *19*(6*), 1-9. https://doi.org/10.1007/s11910-019-0949-4*

Kramer, S. M., Johnson, L. P., Bernhardt, J. P., & Cumming, T. P. (2016). Energy expenditure and cost during walking after stroke: A systematic review. *Archives of Physical Medicine and Rehabilitation, 97*(4), 619-632.e611. https://doi.org/10.1016/j.apmr.2015.11.007

Kuriakose, D., & Xiao, Z. (2020). Pathophysiology and treatment of stroke: Present status and future perspectives. *International Journal of Molecular Sciences*, *21*(20), 7609–7632. https://doi.org/10.3390/ijms21207609

Kwakkel, G., Lannin, N. A., Borschmann, K., English, C., Ali, M., Churilov, L., Saposnik, G., Winstein, C., Van Wegen, E. E. H., Wolf, S. L., Krakauer, J. W., & Bernhardt, J. (2017). Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *Neurorehabilitation and Neural Repair*, *31*(9), 784-792. https://doi.org/10.1177/1545968317732662

Kwakkel, G. P., Veerbeek, J. M. M., van Wegen, E. E. H. P., & Wolf, S. L. P. (2015). Constraint-induced movement therapy after stroke. *Lancet Neurology*, *14*(2), 224-234. https://doi.org/10.1016/S1474-4422(14)70160-7

Laktate. (2013). *Lactate Pro 2 blood lactate test meter operating manual*. Retrieved 18 September from http://www.laktate.com/wp-content/uploads/2013/10/Lactate-Pro-2-Operating-Manual-2.pdf

Lang, C. E., Edwards, D. F., Birkenmeier, R. L., & Dromerick, A. W. (2008). Estimating Minimal Clinically Important Differences of Upper-Extremity Measures Early After Stroke. *Archives of Physical Medicine and Rehabilitation, 89*(9), 1693–1700. https://doi.org/10.1016/j.apmr.2008.02.022

Langhorne, P., Bernhardt, J., & Kwakkel, G. (2011). Stroke care 2: Stroke rehabilitation. *The Lancet*, *377*(9778), 1693-. https://doi.org/10.1016/S0140-6736(11)60325-5

Lasek-Bal, A., Jędrzejowska-Szypułka, H., Różycka, J., Bal, W., Holecki, M., Duława, J., & Lewin-Kowalik, J. (2015). Low concentration of BDNF in the acute phase of ischemic stroke as a factor in poor prognosis in terms of functional status of patients. *Medical Science Monitor*, *21*, 3900–3905. https://doi.org/10.12659/MSM.895358

Lau, C., Chitussi, D., Elliot, S., Giannone, J., McMahon, M. K., Sibley, K. M., Tee, A., Matthews, J., & Salbach, N. (2016). Facilitating community-based exercise for people

with stroke: Cross-sectional e-survey of physical therapist practice and perceived needs. *Physical Therapy, 96*(4), 469–478. https://doi.org/10.2522/ptj.20150117

Lawrence, L. M., Bishop, A., & Curran, J. (2019). Integrated knowledge translation with public health policy makers: A scoping review. *Healthcare Policy*, *14*(3), 55–77. https://doi.org/10.12927/hcpol.2019.25792

Leckie, R. L., Oberlin, L. E., Voss, M. W., Prakash, R. S., Szabo-Reed, A., Chaddock-Heyman, L., Phillips, S. M., Gothe, N. P., Mailey, E., Vieira-Potter, V. J., Martin, S. A., Pence, B. D., Lin, M., Parasuraman, R., Greenwood, P. M., Fryxell, K. J., Woods, J. A., McAuley, E., Kramer, A. F., & Erickson, K. I. (2014). BDNF mediates improvements in executive function following a 1-year exercise intervention. *Frontiers in Human Neuroscience*, 8, 985–985. https://doi.org/10.3389/fnhum.2014.00985

Lee, C. D., Folsom, A. R., & Blair, S. N. (2003). Physical activity and stroke risk: A meta-analysis. *Stroke*, *34*(10), 2475-2481. https://doi.org/10.1161/01.STR.0000091843.02517.9D

Lee, H. J., Moon, H. I., Kim, J. S., & Yi, T. I. (2019). Is there a dose-dependent effect of modified constraint-induced movement therapy in patients with hemiplegia? *NeuroRehabilitation*, *45*(1), 57-66. https://doi.org/10.3233/NRE-192721

Lemos, J. J. R., Alves, C. R., de Souza, S. B. C., Marsiglia, J. D. C., Silva, M. S. M., Pereira, A. C., Teixeira, A. L., Vieira, E. L. M., Krieger, J. E., Negrão, C. E., Alves, G. B., de Oliveira, E. M., Bolani, W., Dias, R. G., & Trombetta, I. C. (2016). Peripheral vascular reactivity and serum BDNF responses to aerobic training are impaired by the BDNF Val66Met polymorphism. *Physiological Genomics*, *48*(2), 116-123. https://doi.org/10.1152/physiolgenomics.00086.2015

Lennon, O. C., Doody, C., Ni Choisdealbh, C., & Blake, C. (2013). Barriers to healthy-lifestyle participation in stroke: Consumer participation in secondary prevention design. *International Journal of Rehabilitation Research*, *36*(4), 354–361. https://doi.org/10.1097/MRR.0b013e3283643d48

Levinger, I., Goodman, C., Matthews, V., Hare, D. L., Jerums, G., Garnham, A., & Selig S. (2008). BDNF, metabolic risk factors, and resistance training in middle-aged individuals. *Medicine and Science in Sports and Exercise, 40*(3), 535-541. https://doi.org/10.1249/MSS.0b013e31815dd057

Li, K.-Y., Lin, K.-C., Wang, T.-N., Wu, C.-Y., Huang, Y.-H., & Ouyang, P. (2012). Ability of three motor measures to predict functional outcomes reported by stroke patients after rehabilitation. *NeuroRehabilitation, 30*(4), 267–275. https://doi.org/10.3233/NRE-2012-0755

Liepert, J., Bauder, H., Wolfgang, H. R., Miltner, W. H., Taub, E., & Weiller, C. (2000). Treatment-induced cortical reorganization after stroke in humans. *Stroke*, *31*(6), 1210-1216. https://doi.org/10.1161/01.STR.31.6.1210

Liepert, J., Hamzei, F., & Weiller, C. (2004). Lesion-induced and training-induced brain reorganization. *Restorative Neurology and Neuroscience*, *22*(3-5), 269-277.

Lieshout, E. C. C. van, van de Port, I. G., Dijkhuizen, R. M., & Visser-Meily, J. M. A. (2020). Does upper limb strength play a prominent role in health-related quality of life in stroke patients discharged from inpatient rehabilitation? *Topics in Stroke Rehabilitation*, *27*(7), 525–533. https://doi.org/10.1080/10749357.2020.1738662

Liljehult, M. M., Euler-Chelpin, M. C., Christensen, T., Buus, L., Stokholm, J., & Rosthøj, S. (2021). Sex differences in independence in activities of daily living early in stroke rehabilitation. *Brain and Behavior*, *11*(8), e2223–n/a. https://doi.org/10.1002/brb3.2223

Limaye, N. S., Carvalho, L. B., & Kramer, S. (2021). Effects of aerobic exercise on serum biomarkers of neuroplasticity and brain repair in stroke: A systematic review. *Archives of Physical Medicine and Rehabilitation*, *102*(8), 1633-1644. https://doi.org/10.1016/j.apmr.2021.04.010

Lindgren, A., & Maguire, J. (2016). Stroke recovery genetics. *Stroke*, *47*(9), 2427-2434. https://doi.org/10.1161/STROKEAHA.116.010648

Liu, W., Wang, X., O'Connor, M., Wang, G., & Han, F. (2020). Brain-derived neurotrophic factor and its potential therapeutic role in stroke comorbidities. *Neural Plasticity*, *2020*, 1969482-1969413. https://doi.org/10.1155/2020/1969482

Lommatzsch, M., Zingler, D., Schuhbaeck, K., Schloetcke, K., Zingler, C., Schuff-Werner, P., & Virchow, J. C. (2005). The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiology of Aging*, *26*(1), 115–123. https://doi.org/10.1016/j.neurobiolaging.2004.03.002

Lucas, S. J., Cotter, J. D., Brassard, P., & Bailey, D. M. (2015). High-intensity interval exercise and cerebrovascular health: Curiosity, cause, and consequence. *Journal of Cerebral Blood Flow & Metabolism, 35*(6), 902–911. https://doi.org/10.1038/jcbfm.2015.49

Luo, W., Liu, T., Li, S., Wen, H., Zhou, F., Zafonte, R., Luo, X., Xu, M., Black-Schaffer, R., Wood, L. J., Wang, Y., & Wang, Q. M. (2019). The serum BDNF level offers minimum predictive value for motor function recovery after stroke. *Translational Stroke Research*, *10*(4), 342-351. https://doi.org/10.1007/s12975-018-0648-5

MacKay-Lyons, M., Billinger, S. A., Eng, J. J., Dromerick, A., Giacomantonio, N., Hafer-Macko, C., Macko, R., Nguyen, E., Prior, P., Suskin, N., Tang, A., Thornton, M., & Unsworth, K. (2020). Aerobic exercise recommendations to optimize best practices in care after stroke: Aerobics 2019 update. *Physical Therapy*, *100*(1), 149-156. https://doi.org/10.1093/ptj/pzz153

Mackay, C. P., Brauer, S. G., Kuys, S. S., Schaumberg, M. A., & Leow, L.-A. (2021). The acute effects of aerobic exercise on sensorimotor adaptation in chronic stroke. *Restorative Neurology and Neuroscience, 39*(5), 367-377. https://doi.org/10.3233/RNN-211175

Mackay, C. P., Kuys, S. S., & Brauer, S. G. (2017). The effect of aerobic exercise on brain-derived neurotrophic factor in people with neurological disorders: A systematic review and meta-analysis. *Neural Plasticity*, *2017*, 4716197-4716199. https://doi.org/10.1155/2017/4716197

Macko., R. (2016). Stroke, brain trauma, and spinal cord injuries. In Moore, G. E., Durstine, J. L., & Painter, P. L. (Ed.), *ACSM's exercise management for persons with chronic disease and disabilities* (pp. 237-248). Human Kinetics.

MacLellan, C. L., Keough, M. B., Granter-Button, S., Chernenko, G. A., Butt, S., & Corbett, D. (2011). A critical threshold of rehabilitation involving brain-derived neurotrophic factor is required for poststroke recovery. *Neurorehabilitation and Neural Repair*, *25*(8), 740-748. https://doi.org/10.1177/1545968311407517

Magistretti, P. J., & Allaman, I. (2018). Lactate in the brain: from metabolic end-product to signalling molecule. *Nature Reviews Neuroscience*, *19*(4), 235–249. https://doi.org/10.1038/nrn.2018.19

Mandehgary Najafabadi, M., Azad, A., Mehdizadeh, H., Behzadipour, S., Fakhar, M., Taghavi Azar Sharabiani, P., Parnianpour, M., Taghizadeh, G., & Khalaf, K. (2019). Improvement of upper limb motor control and function after competitive and

noncompetitive volleyball exercises in chronic stroke survivors: A randomized clinical trial. *Archives of Physical Medicine and Rehabilitation*, *100*(3), 401-411. https://doi.org/10.1016/j.apmr.2018.10.012

Mang, C. S., Campbell, K. L., Ross, C. J. D., & Boyd, L. A. (2013). Promoting neuroplasticity for motor rehabilitation after stroke: Considering the effects of aerobic exercise and genetic variation on brain-derived neurotrophic factor. *Physical Therapy*, *93*(12), 1707-1716. https://doi.org/10.2522/ptj.20130053

Mang, C. S., Snow, N. J., Campbell, K. L., Ross, C. J. D., & Boyd, L. A. (2014). A single bout of high-intensity aerobic exercise facilitates response to paired associative stimulation and promotes sequence-specific implicit motor learning. *Journal of Applied Physiology*, *117*(11), 1325-1336. https://doi.org/10.1152/japplphysiol.00498.2014

Manganotti, P., Patuzzo, S., Cortese, F., Palermo, A., Smania, N., & Fiaschi, A. (2002). Motor disinhibition in affected and unaffected hemisphere in the early period of recovery after stroke. *Clinical Neurophysiology*, *113*(6), 936-943. https://doi.org/10.1016/S1388-2457(02)00062-7

Margineanu, M. B., Mahmood, H., Fiumelli, H., & Magistretti, P. J. (2018). L-lactate regulates the expression of synaptic plasticity and neuroprotection genes in cortical neurons: A transcriptome analysis. *Frontiers in Molecular Neuroscience*, *11*, 375-375. https://doi.org/10.3389/fnmol.2018.00375

Mark, V. W., Taub, E., & Morris, D. M. (2006). Neuroplasticity and constraint-induced movement therapy. *Europa Medicophysica*, *42*(3), 269.

Marosi, K., & Mattson, M. P. (2014). BDNF mediates adaptive brain and body responses to energetic challenges. *Trends in Endocrinology and Metabolism*, *25*(2), 89-98. https://doi.org/10.1016/j.tem.2013.10.006

Marsden, D.L., Dunn, A., Callister, R., McElduff, P., Levi, C. R., & Spratt, N. J. (2017). Interval circuit training for cardiorespiratory fitness is feasible for people after stroke. *International Journal of Therapy and Rehabilitation*, *24*(5), 190–202. https://doi.org/10.12968/ijtr.2017.24.5.190

Mathiowetz, V., Volland, G., Kashman, N., & Weber, K. (1985). Adult norms for the Box and Block Test of manual dexterity. *The American Journal of Occupational Therapy*, *39*(6), 386–391. https://doi.org/10.5014/ajot.39.6.386

Matthews, V. B., Åström, M.-B., Chan, M. H. S., Bruce, C. R., Krabbe, K. S., Prelovsek, O., Åkerström, T., Yfanti, C., Broholm, C., Mortensen, O. H., Penkowa, M., Hojman, P., Zankari, A., Watt, M. J., Bruunsgaard, H., Pedersen, B. K., & Febbraio, M. A. (2009). Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. *Diabetologia, 52*(7), 1409–1418. https://doi.org/10.1007/s00125-009-1364-1

Matozinho, C. V. O., Teixeira-Salmela, L. F., Samora, G. A. R., Sant'Anna, R., Faria, C. D. C. M., & Scianni, A. (2021). Incidence and potential predictors of early onset of upper-limb contractures after stroke. *Disability and Rehabilitation*, *43*(5), 678-684. https://doi.org/10.1080/09638288.2019.1637949

McCluskey, A., Massie, L., Gibson, G., Pinkerton, L., & Vandenberg, A. (2020). Increasing the delivery of upper limb constraint-induced movement therapy post-stroke: A feasibility implementation study. *Australian Occupational Therapy Journal*, *67*(3), 237-249. https://doi.org/10.1111/1440-1630.12647

McKenzie, J. E., Brennan, S. E., Ryan, R. E., Thomson, H. J., & Johnston, R. V. (2021). Chapter 9: Summarizing study characteristics and preparing for synthesis. Cochrane. https://training.cochrane.org/handbook/current/chapter-09

McKim, C. A. (2017). The value of mixed methods research: A mixed methods study. *Journal of Mixed Methods Research, 11*(2), 202–222. https://doi.org/10.1177/1558689815607096

McNulty, P. A., Lin, G., & Doust, C. G. (2014). Single motor unit firing rate after stroke is higher on the less-affected side during stable low-level voluntary contractions. *Frontiers in Human Neuroscience*, *8*, 518–518. https://doi.org/10.3389/fnhum.2014.00518

McNulty, P. A., Thompson-Butel, A. G., Faux, S. G., Lin, G., Katrak, P. H., Harris, L. R., & Shiner, C. T. (2015). The efficacy of wii-based movement therapy for upper limb rehabilitation in the chronic poststroke period: A randomized controlled trial. *International Journal of Stroke*, *10*(8), 1253-1260. https://doi.org/10.1111/ijs.12594

Medical Board. (2020). Good medical practice: A code of conduct for doctors in Australia. Medical Board. Retrieved 29 September 2023 from https://www.medicalboard.gov.au/codes-guidelines-policies/code-of-conduct.aspx

Mezzani, A., Hamm, L. F., Jones, A. M., McBride, P. E., Moholdt, T., Stone, J. A., Urhausen, A., & Williams, M. A. (2012). Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: A joint position statement of the European Association for Cardiovascular Prevention And Rehabilitation, the American Association Of Cardiovascular And Pulmonary Rehabilitation, and the Canadian Association Of Cardiac Rehabilitation. *Journal of Cardiopulmonary Rehabilitation and Prevention*, *32*(6), 327–350. https://doi.org/10.1097/HCR.0b013e3182757050

Miller, K. K., Porter, R. E., DeBaun-Sprague, E., Van Puymbroeck, M., & Schmid, A. A. (2017). Exercise after stroke: Patient adherence and beliefs after discharge from rehabilitation. *Topics in Stroke Rehabilitation*, *24*(2), 142-148. https://doi.org/10.1080/10749357.2016.1200292

Milot, M. H., & Cramer, S. C. (2008). Biomarkers of recovery after stroke. *Current Opinion in Neurology*, *21*(6), 654-659. https://doi.org/10.1097/WCO.0b013e3283186f96

Miltner, W. H. R., Bauder, H., & Taub, E. (2016). Change in movement-related cortical potentials following constraint-induced movement therapy (CIMT) after stroke. *Zeitschrift für Psychologie*, *224*(2), 112-124. https://doi.org/10.1027/2151-2604/a000245

Minozzi, S., Cinquini, M., Gianola, S., Gonzalez-Lorenzo, M., & Banzi, R. (2020). The revised Cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application. *Journal of Clinical Epidemiology, 126*, 37-44. https://doi.org/10.1016/j.jclinepi.2020.06.015

Mirowska-Guzel, D., Gromadzka, G., Czlonkowski, A., & Czlonkowska, A. (2012). BDNF − 270 C>T polymorphisms might be associated with stroke type and BDNF − 196 G>A corresponds to early neurological deficit in hemorrhagic stroke. *Journal of Neuroimmunology, 249*(1), 71–75. https://doi.org/10.1016/j.jneuroim.2012.04.011

Mirowska-Guzel, D., Gromadzka, G., Mendel, T., Janus-Laszuk, B., Dzierka, J., Sarzynska-Dlugosz, I., Czlonkowski, A., & Czlonkowska, A. (2014). Impact of BDNF -196 G>A and BDNF -270 C>T polymorphisms on stroke rehabilitation outcome: Sex and age differences. *Topics in Stroke Rehabilitation*, *21*(sup1), S33–S41. https://doi.org/10.1310/tsr21S1-S33

Mirza, M., Siebert, S., Pratt, A., Insch, E., McIntosh, F., Paton, J., Wright, C., Buckley, C. D., Isaacs, J., McInnes, I. B., Raza, K., & Falahee, M. (2022). Impact of the COVID-19

pandemic on recruitment to clinical research studies in rheumatology. *Musculoskeletal Care, 20*(1), 209–213. https://doi.org/10.1002/msc.1561

Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P., Elbourne, D., Egger, M., Altman, D. G., & CONSORT. (2012). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery, 10*(1), 28–55. https://doi.org/10.1016/j.ijsu.2011.10.001

Molinari, C., Morsanuto, V., Ruga, S., Notte, F., Farghali, M., Galla, R., & Uberti, F. (2020). The role of BDNF on aging-modulation markers. *Brain Sciences*, *10*(5), 285-. https://doi.org/10.3390/brainsci10050285

Mojtabavi, H., Shaka, Z., Momtazmanesh, S., Ajdari, A., & Rezaei, N. (2022). Circulating brain-derived neurotrophic factor as a potential biomarker in stroke: A systematic review and meta-analysis. *Journal of Translational Medicine, 20*(1), 126-126. https://doi.org/10.1186/s16967-02203312-y

Molendijk, M. L., Haffmans, J. P., Bus, B. A. A., Spinhoven, P., Penninx, B. W. J. H., Prickaerts, J., Oude Voshaar, R. C., & Elzinga, B. M. (2012). Serum BDNF concentrations show strong seasonal variation and correlations with the amount of ambient sunlight. *PloS One*, *7*(11), e48046-e48046. https://doi.org/10.1371/journal.pone.0048046

Molle Da Costa, R. D., Luvizutto, G. J., Martins, L. G., Thomaz De Souza, J., Regina Da Silva, T., Alvarez Sartor, L. C., Winckler, F. C., Modolo, G. P., Molle, E. R. D. S. D., Dos Anjos, S. M., Bazan, S. G. Z., Cuadrado, L. M., & Bazan, R. (2019). Clinical factors associated with the development of nonuse learned after stroke: A prospective study. *Topics in Stroke Rehabilitation*, *26*(7), 511-517. https://doi.org/10.1080/10749357.2019.1631605

Moncion, K., Biasin, L., Jagroop, D., Bayley, M., Danells, C., Mansfield, A., Salbach, N. M., Inness, E., & Tang, A. (2020). Barriers and facilitators to aerobic exercise implementation in stroke rehabilitation: A scoping review. *Journal of Neurologic Physical Therapy*, *44*(3), 179–187. https://doi.org/10.1097/NPT.0000000000000318

Moore, G. E., Durstine, J. L., & Painter, P. L. (2016). Exercise is medicine in chronic care. In A. T. Tocco (Ed.), *ACSM's exercise management for persons with chronic diseases and disabilities* (4th ed. ed., pp. 3-14). Human Kinetics.

Morris, D. M., Taub, E., & Mark, V. W. (2006). Constraint-induced movement therapy: Characterizing the intervention protocol. *Europa Medicophysica*, *42*(3), 257.

Mourad, M., Bousleiman, S., Wapner, R., & Gyamfi-Bannerman, C. (2020). Conducting research during the COVID-19 pandemic. *Seminars in Perinatology, 44*(7), 151287–151287. https://doi.org/10.1016/j.semperi.2020.151287

Mueller, P., Duderstadt, Y., Lessmann, V., & Mueller, N. G. (2020). Lactate and BDNF: Key mediators of exercise induced neuroplasticity? *Journal of Clinical Medicine*, *9*(4), 1136. https://doi.org/10.3390/jcm9041136

Namey, E., Guest, G., McKenna, K., & Chen, M. (2016). Evaluating bang for the buck: a cost-effectiveness comparison between individual interviews and focus groups based on thematic saturation levels. *The American Journal of Evaluation*, *37*(3), 425–440. https://doi.org/10.1177/1098214016630406

Nascimento, L. R., Boening, A., Galli, A., Polese, J. C., & Ada, L. (2021). Treadmill walking improves walking speed and distance in ambulatory people after stroke and is not inferior to overground walking: A systematic review. *Journal of Physiotherapy*, *67*(2), 95–104. https://doi.org/10.1016/j.jphys.2021.02.014

Nathoo, C., Buren, S., El-Haddad, R., Feldman, K., Schroeder, E., Brooks, D., Inness, E. L., & Marzolini, S. (2018). Aerobic training in Canadian stroke rehabilitation programs. *Journal of Neurologic Physical Therapy, 42*(4), 248–255. https://doi.org/10.1097/NPT.0000000000000237

National Institutes of Health. (2003). *NIH Stroke Scale*. Retrieved 18 August from https://www.stroke.nih.gov/documents/NIH_Stroke_Scale_508C.pdf

Nepveu, J.-F., Thiel, A., Tang, A., Fung, J., Lundbye-Jensen, J., Boyd, L. A., & Roig, M. (2017). A single bout of high-intensity interval training improves motor skill retention in individuals with stroke. *Neurorehabilitation and Neural Repair*, *31*(8), 726-735. https://doi.org/10.1177/1545968317718269

Nguyen, T., Graham, I. D., Mrklas, K. J., Bowen, S., Cargo, M., Estabrooks, C. A., Kothari, A., Lavis, J., Macaulay, A. C., MacLeod, M., Phipps, D., Ramsden, V. R., Renfrew, M. J., Salsberg, J., & Wallerstein, N. (2020). How does integrated knowledge translation (IKT) compare to other collaborative research approaches to generating and

translating knowledge? Learning from experts in the field. *Health Research Policy and Systems*, *18*(1), 35–35. https://doi.org/10.1186/s12961-020-0539-6

Nicholson, S. L., Donaghy, M., Johnston, M., Sniehotta, F. F., van Wijck, F., Johnston, D., Greig, C., McMurdo, M. E. T., & Mead, G. (2014). A qualitative theory guided analysis of stroke survivors' perceived barriers and facilitators to physical activity. *Disability and Rehabilitation*, *36*(22), 1857-1868. https://doi.org/10.3109/09638288.2013.874506

Nicholson, S. L., Greig, C. A., Sniehotta, F., Johnston, M., Lewis, S. J., McMurdo, M. E., Johnston, D., Scopes, J., & Mead, G. E. (2017). Quantitative data analysis of perceived barriers and motivators to physical activity in stroke survivors. *The Journal of the Royal College of Physicians of Edinburgh*, *47*(3), 231–236. https://doi.org/10.4997/JRCPE.2017.304

Nicholson, S., Sniehotta, F. F., van Wijck, F., Greig, C. A., Johnston, M., McMurdo, M. E. T., Dennis, M., & Mead, G. E. (2013). A systematic review of perceived barriers and motivators to physical activity after stroke. *International Journal of Stroke, 8*(5), 357–364. https://doi.org/10.1111/j.1747-4949.2012.00880.x

Nijland, R., van Wegen, E., van der Krogt, H., Bakker, C., Buma, F., Klomp, A., van Kordelaar, J., & Kwakkel, G. (2013). Characterizing the protocol for early modified constraint-induced movement therapy in the EXPLICIT-stroke trial. *Physiotherapy Research International: The Journal for Researchers and Clinicians in Physical Therapy*, *18*(1), 1-15. https://doi.org/10.1002/pri.1521

Nursing and Midwifery Board of Australia. (2016). Registered nurse standards for practice. Nursing and Midwifery Board of Australia. Retrieved 29 September 2023 from https://www.nursingmidwiferyboard.gov.au/Codes-Guidelines-Statements/Professional-standards.aspx#

O'Cathain, A., Murphy, E., & Nicholl, J. (2007). Why, and how, mixed methods research is undertaken in health services research in England: A mixed methods study. *BMC Health Services Research, 7*(1), 85–85. https://doi.org/10.1186/1472-6963-7-85

O'Cathain, A., Murphy, E., & Nicholl, J. (2010). Three techniques for integrating data in mixed methods studies. *BMJ, 341*(7783), 1147–1150. https://doi.org/10.1136/bmj.c4587

Obembe, A. O., Simpson, L. A., & Eng, J. J. (2023). The relationship between Rating of Everyday Arm-use in the Community and Home (REACH) scale affected arm-use assessment, activity and participation after stroke. *Physiotherapy Research International: The Journal for Researchers and Clinicians in Physical Therapy,* e2010–e2010. https://doi.org/10.1002/pri.2010

Occupational Therapy Australia. (2017). Position paper: Occupational therapy scope of practice framework. Occupational Therapy Australia. Retrieved 29 September 2023 from https://otaus.com.au/publicassets/725829df-2503-e911-a2c2-b75c2fd918c5/Occupational%20Therapy%20Scope%20of%20Practice%20Framework%20(June%202017).pdf

O'Donnell, M. J. D., Xavier, D. P., Liu, L. P., Zhang, H. P., Chin, S. L., Rao-Melacini, P. M., Rangarajan, S. M., Islam, S. M., Pais, P. P., McQueen, M. J. P., Mondo, C. M. D., Damasceno, A. P., Lopez-Jaramillo, P. P., Hankey, G. J. P., Dans, A. L. P., Yusoff, K. P., Truelsen, T. D., Diener, H.-C. P., Sacco, R. L. P., . . . Yusuf, S. P. (2010). Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. *The Lancet (British edition)*, *376*(9735), 112-123. https://doi.org/10.1016/S0140-6736(10)60834-3

Ostadan, F., Centeno, C., Daloze, J.-F., Frenn, M., Lundbye-Jensen, J., & Roig, M. (2016). Changes in corticospinal excitability during consolidation predict acute exercise-induced off-line gains in procedural memory. *Neurobiology of Learning and Memory*, *136*, 196–203. https://doi.org/10.1016/j.nlm.2016.10.009

Overman, J. J., & Carmichael, S. T. (2014). Plasticity in the injured brain: More than molecules matter. *The Neuroscientist*, *20*(1), 15–28. https://doi.org/10.1177/1073858413491146

Ozan, E., Okur, H., Eker, Ç., Eker, Ö. D., Gönül, A. S., & Akarsu, N. (2009). The effect of depression, BDNF gene val66met polymorphism and gender on serum BDNF levels. *Brain Research Bulletin*, *81*(1), 61-65. https://doi.org/10.1016/j.brainresbull.2009.06.022

Page, S. J., Fulk, G. D., & Boyne, P. (2012). Clinically important differences for the Upper-Extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to

chronic stroke. *Physical Therapy, 92*(6), 791–798. https://doi.org/10.2522/ptj.20110009

Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., Stewart, L. A., Thomas, J., Tricco, A. C., Welch, V. A., Whiting, P., & McKenzie, J. E. (2021). PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ*, *372*, n160. https://doi.org/10.1136/bmj.n160

Page, S. (2003). Forced use after TBI: promoting plasticity and function through practice. *Brain Injury, 17*(8), 675–684. https://doi.org/10.1080/0269905031000107160

Page, S. J., Levine, P., & Leonard, A. C. (2005). Modified constraint-induced therapy in acute stroke: A randomized controlled pilot study. *Neurorehabilitation and Neural Repair*, *19*(1), 27-32. https://doi.org/10.1177/1545968304272701

Page, S. J., Sisto, S., Levine, P., & McGrath, R. E. (2004). Efficacy of modified constraint-induced movement therapy in chronic stroke: A single-blinded randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, *85*(1), 14-18. https://doi.org/10.1016/S0003-9993(03)00481-7

Page, S. J., Sisto, S. A., Levine, P., Johnston, M. V., & Hughes, M. (2001). Modified constraint induced therapy: A randomized feasibility and efficacy study. *Journal of Rehabilitation Research and Development*, *38*(5), 583-590.

Pang, M. Y. C., Eng, J. J., Dawson, A. S., & Gylfadóttir, S. (2006). The use of aerobic exercise training in improving aerobic capacity in individuals with stroke: A meta-analysis. *Clinical Rehabilitation*, *20*(2), 97-111. https://doi.org/10.1191/0269215506cr926oa

Patridge, E. F., & Bardyn, T. P. (2018). Research Electronic Data Capture (REDCap). *Journal of the Medical Library Association, 106*(1), 142–144. https://doi.org/10.5195/jmla.2018.319

Pearce, G., Pinnock, H., Epiphaniou, E., Parke, H. L., Heavey, E., Griffiths, C. J., Greenhalgh, T., Sheikh, A., & Taylor, S. J. C. (2015). Experiences of Self-management support following a stroke: A meta-review of qualitative systematic reviews. *PloS One*, *10*(12), e0141803–e0141803. https://doi.org/10.1371/journal.pone.0141803

Pedard, M., Brenière, C., Pernet, N., Vergely, C., Béjot, Y., & Marie, C. (2018). Brain-derived neurotrophic factor in peripheral blood mononuclear cells and stroke outcome. *Experimental Biology and Medicine*, *243*(15-16), 1207-1211. https://doi.org/10.1177/1535370218815612

Pedersen, P. M., Jørgensen, H. S., Nakayama, H., Raaschou, H. O., & Olsen, T. S. (1998). Impaired orientation in acute stroke: frequency, determinants, and time-course of recovery. The Copenhagen Stroke Study. *Cerebrovascular Diseases, 8*(2), 90–96. https://doi.org/10.1159/000015824

Pendlebury, S. T., Giles, M. F., & Rothwell, P. M. (2009). Epidemiology, risk factors, pathophysiology and causes of transient ischemic attacks and stroke. In *Transient ischemic attack and stroke diagnosis, investigation and management.* Cambridge University Press.

Perneger, T. V., Courvoisier, D. S., Hudelson, P. M., & Gayet-Ageron, A. (2015). Sample size for pre-tests of questionnaires. *Quality of Life Research, 24*(1), 147–151. https://doi.org/10.1007/s11136-014-0752-2

Petchenik, J., & Watermolen, D. J. (2011). A cautionary note on using the internet to survey recent hunter education graduates. *Human Dimensions of Wildlife, 16*(3), 216–218. https://doi.org/10.1080/10871209.2011.563434

Pikula, A., Beiser, A. S., Vasan, R. S., Seshadri, S., Chen, T. C., Preis, S. R., Vorgias, D., Decarli, C., Au, R., Kelly-Hayes, M., Kase, C. S., & Wolf, P. A. (2013). Serum brain-derived neurotrophic factor and vascular endothelial growth factor levels are associated with risk of stroke and vascular brain injury: Framingham study. *Stroke*, *44*(10), 2768-2775. https://doi.org/10.1161/STROKEAHA.113.001447

Pin-Barre, C., Hugues, N., Constans, A., Berton, E., Pellegrino, C., & Laurin, J. (2021). Effects of different high-intensity interval training regimens on endurance and neuroplasticity after cerebral ischemia. *Stroke, 52*(3), 1109–1114. https://doi.org/10.1161/STROKEAHA.120.031873

Plant, S. E., Tyson, S. F., Kirk, S., & Parsons, J. (2016). What are the barriers and facilitators to goal-setting during rehabilitation for stroke and other acquired brain injuries? A systematic review and meta-synthesis. *Clinical Rehabilitation*, *30*(9), 921–930. https://doi.org/10.1177/0269215516655856

Ploughman, M., Attwood, Z., White, N., Doré, J. J. E., & Corbett, D. (2007). Endurance exercise facilitates relearning of forelimb motor skill after focal ischemia: Endurance exercise facilitates forelimb recovery. *The European Journal of Neuroscience, 25*(11), 3453-3460. https://doi.org/10.1111/j.1460-9568.2007.05591.x

Ploughman, M., Austin, M. W., Glynn, L., & Corbett, D. (2015). The effects of poststroke aerobic exercise on neuroplasticity: A systematic review of animal and clinical studies. *Translational Stroke Research*, *6*(1), 13-28. https://doi.org/10.1007/s12975-014-0357-7

Ploughman, M., Eskes, G. A., Kelly, L. P., Kirkland, M. C., Devasahayam, A. J., Wallack, E. M., Abraha, B., Hasan, S. M. M., Downer, M. B., Keeler, L., Wilson, G., Skene, E., Sharma, I., Chaves, A. R., Curtis, M. E., Bedford, E., Robertson, G. S., Moore, C. S., McCarthy, J., & Mackay-Lyons, M. (2019). Synergistic benefits of combined aerobic and cognitive training on fluid intelligence and the role of IGF-1 in chronic stroke. *Neurorehabilitation and Neural Repair*, *33*(3), 199-212. https://doi.org/10.1177/1545968319832605

Ploughman, M., & Kelly, L. P. (2016). Four birds with one stone? Reparative, neuroplastic, cardiorespiratory, and metabolic benefits of aerobic exercise poststroke. *Current Opinion in Neurology*, *29*(6), 684-692. https://doi.org/10.1097/WCO.0000000000000383

Ploughman, M., Windle, V., Maclellan, C. L., White, N., Doe, J. J., & Corbett, D. (2009). Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats. *Stroke*, *40*(4), 1490-1495. https://doi.org/10.1161/STROKEAHA.108.531806

Polacchini, A., Metelli, G., Francavilla, R., Baj, G., Florean, M., Mascaretti, L. G., & Tongiorgi, E. (2015). A method for reproducible measurements of serum BDNF: Comparison of the performance of six commercial assays. *Scientific Reports*, *5*(1), 17989-17989. https://doi.org/10.1038/srep17989

Pollock, A., Farmer, S. E., Brady, M. C., Langhorne, P., Mead, G. E., Mehrholz, J., & van Wijck, F. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database of Systematic Reviews*(11), CD010820-CD010820. https://doi.org/10.1002/14651858.CD010820.pub2

Portney, L. G. (2020). Designing surveys and questionnaires. In F.A. Davis (Eds.), *Foundations of clinical research: Applications to evidence-based practice* (Fourth edition.) (pp. 141-158).

Prout, E. C., Mansfield, A., McIlroy, W. E., & Brooks, D. (2017). Patients' perspectives on aerobic exercise early after stroke. *Disability and Rehabilitation, 39*(7), 684–690. https://doi.org/10.3109/09638288.2016.1161833

Preston, E., Dean, C. M., Ada, L., Stanton, R., Brauer, S., Kuys, S., & Waddington, G. (2017). Promoting physical activity after stroke via self-management: A feasibility study. *Topics in Stroke Rehabilitation*, *24*(5), 353-360. https://doi.org/10.1080/10749357.2017.1304876

Putaala, J. (2016). Ischemic stroke in the young: Current perspectives on incidence, risk factors, and cardiovascular prognosis. *European Stroke Journal*, *1*(1), 28-40. https://doi.org/10.1177/2396987316629860

Qiao, H.-J., Li, Z.-Z., Wang, L.-M., Sun, W., Yu, J.-C., & Wang, B. (2017). Association of lower serum brain-derived neurotrophic factor levels with larger infarct volumes in acute ischemic stroke. *Journal of Neuroimmunology*, *307*, 69-73. https://doi.org/10.1016/j.jneuroim.2017.04.002

Quaney, B. M., Boyd, L. A., McDowd, J. M., Zahner, L. H., Jianghua, H., Mayo, M. S., & Macko, R. F. (2009). Aerobic exercise improves cognition and motor function poststroke. *Neurorehabilitation and Neural Repair*, *23*(9), 879-885. https://doi.org/10.1177/1545968309338193

Quinlan, E. B., Dodakian, L., See, J., McKenzie, A., Le, V., Wojnowicz, M., Shahbaba, B., & Cramer, S. C. (2015). Neural function, injury, and stroke subtype predict treatment gains after stroke. *Annals of Neurology*, *77*(1), 132-145. https://doi.org/10.1002/ana.24309

Rahayu, U. B., Wibowo, S., Setyopranoto, I., & Romli, M. H. (2020). Effectiveness of physiotherapy interventions in brain plasticity, balance and functional ability in stroke survivors: A randomized controlled trial. *NeuroRehabilitation, 47*(4), 463-470. https://doi.org/10.3233/NRE-203210

Rasmussen, P., Brassard, P., Adser, H., Pedersen, M. V., Leick, L., Hart, E., Secher, N. H., Pedersen, B. K., & Pilegaard, H. (2009). Evidence for a release of brain-derived

neurotrophic factor from the brain during exercise. *Experimental Physiology, 94*(10), 1062-1069. https://doi.org/10.1113/expphysiol.2009.048512

Ražanskas, P., Verikas, A., Olsson, C., & Viberg, P.-A. (2015). Predicting blood lactate concentration and oxygen uptake from sEMG data during Fatiguing cycling exercise. *Sensors*, *15*(8), 20480–20500. https://doi.org/10.3390/s150820480

Regan, E. W., Handlery, R., Stewart, J. C., Pearson, J. L., Wilcox, S., & Fritz, S. (2021). Integrating survivors of stroke Into exercise-based cardiac rehabilitation improves endurance and functional strength. *Journal of the American Heart Association, 10*(3), e017907–e017907. https://doi.org/10.1161/JAHA.120.017907

Rimmer, J. H., Wang, E., & Smith, D. (2008). Barriers associated with exercise and community access for individuals with stroke. *Journal of Rehabilitation Research and Development*, *45*(2), 315-322. https://doi.org/10.1682/JRRD.2007.02.0042

Rinderknecht, M. D., Lambercy, O., Raible, V., Büsching, I., Sehle, A., Liepert, J., & Gassert, R. (2018). Reliability, validity, and clinical feasibility of a rapid and objective assessment of post-stroke deficits in hand proprioception. *Journal of Neuroengineering and Rehabilitation*, *15*(1), 47-47. https://doi.org/10.1186/s12984-018-0387-6

Ritchie, J., & Lewis, J. (2003). Qualitative research practice: A guide for social science students and researchers. SAGE Publications

Rocha, L. S. O., Gama, G. C. B., Rocha, R. S. B., Rocha, L. de B., Dias, C. P., Santos, L. L. S., Santos, M. C. de S., Montebelo, M. I. de L., & Teodori, R. M. (2021). Constraint Induced Movement Therapy Increases Functionality and Quality of Life after Stroke. *Journal of Stroke and Cerebrovascular Diseases*, *30*(6), 105774–105774. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105774

Rognmo, Ø., Hetland, E., Helgerud, J., Hoff, J., & Slørdahl, S. A. (2004). High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *European Journal of Cardiovascular Prevention and Rehabilitation, 11*(3), 216–222. https://doi.org/10.1097/01.hjr.0000131677.96762.0c

Roig, M., Nordbrandt, S., Geertsen, S. S., & Nielsen, J. B. (2013). The effects of cardiovascular exercise on human memory: A review with meta-analysis. *Neuroscience and*

Biobehavioral Reviews, *37*(8), 1645-1666. https://doi.org/10.1016/j.neubiorev.2013.06.012

Roig, M., Skriver, K., Lundbye-Jensen, J., Kiens, B., & Nielsen, J. B. (2012). A single bout of exercise improves motor memory. *PloS One*, *7*(9), e44594-e44594. https://doi.org/10.1371/journal.pone.0044594

Roig, M., Thomas, R., Mang, C. S., Snow, N. J., Ostadan, F., Boyd, L. A., & Lundbye-Jensen, J. (2016). Time-dependent effects of cardiovascular exercise on memory. *Exercise and Sport Sciences Reviews*, *44*(2), 81-88. https://doi.org/10.1249/JES.0000000000000078

Rojas Vega, S., Strüder, H. K., Vera Wahrmann, B., Schmidt, A., Bloch, W., & Hollmann, W. (2006). Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. *Brain Research, 1121*(1), 59-65. https://doi.org/10.1016/j.brainres.2006.08.105

Rose, D., Paris, T., Crews, E., Wu, S. S., Sun, A., Behrman, A. L., & Duncan, P. (2011). Feasibility and effectiveness of circuit training in acute stroke rehabilitation. *Neurorehabilitation and Neural Repair*, *25*(2), 140-148. https://doi.org/10.1177/1545968310384270

Rose, T. A., Worrall, L. E., Hickson, L. M., & Hoffmann, T. C. (2011). Aphasia friendly written health information: Content and design characteristics. *International Journal of Speech Language Pathology*, *13*(4), 335–347. https://doi.org/10.3109/17549507.2011.560396

Rosenfeldt, A. B., Linder, S. M., Davidson, S., Clark, C., Zimmerman, N. M., Lee, J. J., & Alberts, J. L. (2019). Combined aerobic exercise and task practice improve health-related quality of life poststroke: A preliminary analysis. *Archives of Physical Medicine and Rehabilitation*, *100*(5), 923-930. https://doi.org/10.1016/j.apmr.2018.11.011

Ross, K. M., Howe, T., & Jenstad, L. M. (2023). Designing a group yoga class for adults with aphasia: “From the minute you walk in... it is communicatively accessible.” *Aphasiology*, *37*(11), 1798–1817. https://doi.org/10.1080/02687038.2022.2124504

Ruchinskas, R. A., & Curyto, K. J. (2003). Cognitive screening in geriatric rehabilitation. *Rehabilitation Psychology, 48*(1), 14-22. https://doi.org/10.1037/0090-5550.48.1.14

Rutten-Jacobs, L. C. A., Arntz, R. M., Maaijwee, N. A. M., Schoonderwaldt, H. C., Dorresteijn, L. D., van Dijk. E. J., & de Leeuw, F. E. (2015). Cardiovascular disease is the main cause of long-term excess mortality after ischemic stroke in young adults. *Hypertension, 65*(3), 670-675. https://doi.org/10.1161/HYPERTENSIONAHA.114.04895

Ryan, A. S., Xu, H., Ivey, F. M., Macko, R. F., & Hafer-Macko, C. E. (2019). Brain-derived neurotrophic factor, epigenetics in stroke skeletal muscle, and exercise training. *Neurology Genetics*, *5*(3), e331-e331. https://doi.org/10.1212/NXG.0000000000000331

Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J. . (Buddy), Culebras, A., Elkind, M. S. ., George, M. G., Hamdan, A. D., Higashida, R. T., Hoh, B. L., Janis, L. S., Kase, C. S., Kleindorfer, D. O., Lee, J.-M., Moseley, M. E., Peterson, E. D., Turan, T. N., Valderrama, A. L., & Vinters, H. V. (2013). An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, *44*(7), 2064–2089. https://doi.org/10.1161/STR.0b013e318296aeca

Sadler, E., Wolfe, C. D. A., Jones, F., & McKevitt, C. (2017). Exploring stroke survivors' and physiotherapists' views of self-management after stroke: A qualitative study in the UK. *BMJ Open*, *7*(3), e011631-e011631. https://doi.org/10.1136/bmjopen-2016-011631

Sathian, B., Asim, M., Banerjee, I., Pizarro, A. B., Roy, B., Van Teijlingen, E. R., Nascimento, I. J. B. do, & Alhamad, H. K. (2020). Impact of COVID-19 on clinical trials and clinical research: A systematic review. *Nepal Journal of Epidemiology*, *10*(3), 878–887. https://doi.org/10.3126/nje.v10i3.31622

Saunders, D. H., Sanderson, M., Hayes, S., Kilrane, M., Greig, C. A., Brazzelli, M., & Mead, G. E. (2016). Physical fitness training for stroke patients. *Cochrane Database of Systematic Reviews*, *3*, CD003316-CD003316. https://doi.org/10.1002/14651858.CD003316.pub6

Sawaki, L., Butler, A. J., Leng, X., Wassenaar, P. A., Mohammad, Y. M., Blanton, S., Sathian, K., Nichols-Larsen, D. S., Wolf, S. L., Good, D. C., & Wittenberg, G. F. (2014). Differential patterns of cortical reorganization following constraint-induced

movement therapy during early and late period after stroke: A preliminary study. *NeuroRehabilitation 35*(3), 415-426. https://doi.org/10.3233/NRE-141132

Sawaki, L., Butler, A. J., Xiaoyan, L., Wassenaar, P. A., Mohammad, Y. M., Blanton, S., Sathian, K., Nichols-Larsen, D. S., Wolf, S. L., Good, D. C., & Wittenberg, G. F. (2008). Constraint-induced movement therapy results in increased motor map area in subjects 3 to 9 months after stroke. *Neurorehabilitation and Neural Repair*, *22*(5), 505-513. https://doi.org/10.1177/1545968308317531

Scavuzzo, C. J., Rakotovao, I., & Dickson, C. T. (2020). Differential effects of L- and D-lactate on memory encoding and consolidation: Potential role of HCAR1 signaling. *Neurobiology of Learning and Memory*, *168*, 107151-107151. https://doi.org/10.1016/j.nlm.2019.107151

Schabitz, W.-R., Steigleder, T., Cooper-Kuhn, C. M., Schwab, S., Sommer, C., Schneider, A., & Kuhn, H. G. (2007). Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis. *Stroke, 38*(7), 2165-2172. https://doi.org/10.1161/STROKEAHA.106.477331

Schaechter, J. D., Moore, C. I., Connell, B. D., Rosen, B. R., & Dijkhuizen, R. M. (2006). Structural and functional plasticity in the somatosensory cortex of chronic stroke patients. *Brain*, *129*(10), 2722-2733. https://doi.org/10.1093/brain/awl214

Schiffer, T., Schulte, S., Sperlich, B., Achtzehn, S., Fricke, H., & Strüder, H. K. (2011). Lactate infusion at rest increases BDNF blood concentration in humans. *Neuroscience Letters*, *488*(3), 234-237. https://doi.org/10.1016/j.neulet.2010.11.035

Schmidt, M., Jacobsen, J. B., Johnsen, S. P., Bøtker, H. E., & Sørensen, H. T. (2014). Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. *Neurology*, *82*(4), 340-350. https://doi.org/10.1212/WNL.0000000000000062

Schmolesky, M. T., Webb, D. L., & Hansen, R. A. (2013). The effects of aerobic exercise intensity and duration on levels of brain-derived neurotrophic factor in healthy men. *Journal of Sports Science & Medicine*, *12*(3), 502-511.

Schurr, A. (2014). Cerebral glycolysis: A century of persistent misunderstanding and misconception. *Frontiers in Neuroscience*, *8*, 360–360. https://doi.org/10.3389/fnins.2014.00360

See, J., Dodakian, L., Chou, C., Chan, V., McKenzie, A., Reinkensmeyer, D. J., & Cramer, S. C. (2013). A standardized approach to the Fugl-Meyer Assessment and its implications for clinical trials. *Neurorehabilitation and Neural Repair*, *27*(8), 732–741. https://doi.org/10.1177/1545968313491000

Seifert, T., Brassard, P., Wissenberg, M., Rasmussen, P., Nordby, P., Stallknecht, B., Adser, H., Jakobsen, A. H., Pilegaard, H., Nielsen, H. B., & Secher, N. H. (2010). Endurance training enhances BDNF release from the human brain. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 298*(2), 372-377. https://doi.org/10.1152/ajpregu.00525.2009

Sen, S., Duman, R., & Sanacora, G. (2008). Serum brain-derived neurotrophic factor, depression, and antidepressant medications: Meta-analyses and implications. *Biological Psychiatry*, *64*(6), 527-532. https://doi.org/10.1016/j.biopsych.2008.05.005

Sewell, K., Tse, T., Harris, E., Matyas, T., Churilov, L., Ma, H., Davis, S. M., Donnan, G. A., & Carey, L. M. (2021). Pre-existing comorbidity burden and patient perceived stroke impact. *International Journal of Stroke*, *16*(3), 273-279. https://doi.org/10.1177/1747493020920838

Shaughnessy, M., Resnick, B. M., & Macko, R. F. (2006). Testing a model of post-stroke exercise behavior. *Rehabilitation Nursing*, *31*(1), 15-21. https://doi.org/10.1002/j.2048-7940.2006.tb00005.x

Shi, Y. X. M. D., Tian, J. H. P., Yang, K. H. P., & Zhao, Y. P. (2011). Modified constraint-induced movement therapy versus traditional rehabilitation in patients with upper-extremity dysfunction after stroke: A systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *92*(6), 972-982. https://doi.org/10.1016/j.apmr.2010.12.036

Shiggins, C., Ryan, B., O'Halloran, R., Power, E., Bernhardt, J., Lindley, R. I., McGurk, G., Hankey, G. J., & Rose, M. L. (2022). Towards the consistent inclusion of people with aphasia in stroke research irrespective of discipline. *Archives of Physical Medicine and Rehabilitation*, *103*(11), 2256–2263. https://doi.org/10.1016/j.apmr.2022.07.004

Shiner, C. T., Pierce, K. D., Thompson-Butel, A. G., Trinh, T., Schofield, P. R., & McNulty, P. A. (2016). BDNF genotype interacts with motor function to influence rehabilitation responsiveness poststroke. *Frontiers in Neurology*, *7*, 69-69. https://doi.org/10.3389/fneur.2016.00069

Shiner, C. T., Vratsistas-Curto, A., Bramah, V., Faux, S. G., & Watanabe, Y. (2020). Prevalence of upper-limb spasticity and its impact on care among nursing home residents with prior stroke. *Disability and Rehabilitation*, *42*(15), 2170-2177. https://doi.org/10.1080/09638288.2018.1555620

Siahkouhian, M., Khodadadi, D., & Shahmoradi, K. (2013). Effects of high-intensity interval training on aerobic and anaerobic indices: Comparison of physically active and inactive men. *Science and Sports, 28*(5), e119–e125. https://doi.org/10.1016/j.scispo.2012.11.006

Simpson, L. A., & Eng, J. J. (2013). Functional Recovery Following Stroke: Capturing Changes in Upper-Extremity Function. *Neurorehabilitation and Neural Repair, 27*(3), 240–250. https://doi.org/10.1177/1545968312461719

Simpson, L.A., Eng, J. J., Backman, C. L., & Miller, W. C. (2013). Rating of Everyday Arm-Use in the Community and Home (REACH) scale for capturing affected arm-use after stroke: development, reliability, and validity. *PloS One*, *8*(12), e83405–e83405. https://doi.org/10.1371/journal.pone.0083405

Simpson, L. A., Eng, J. J., & Tawashy, A. E. (2011). Exercise perceptions among people with stroke: Barriers and facilitators to participation. *International Journal of Therapy and Rehabilitation*, *18*(9), 520-529. https://doi.org/10.12968/ijtr.2011.18.9.520

Singh, A. M., Duncan, R. E., Neva, J. L., & Staines, W. R. (2014). Aerobic exercise modulates intracortical inhibition and facilitation in a nonexercised upper limb muscle. *BMC Sports Science, Medicine & Rehabilitation*, *6*(1), 23–23. https://doi.org/10.1186/2052-1847-6-23

Singh, A. M., Neva, J. L., & Staines, W. R. (2016). Aerobic exercise enhances neural correlates of motor skill learning. *Behavioural Brain Research*, *301*, 19–26. https://doi.org/10.1016/j.bbr.2015.12.020

Singh, R.-J., Chen, S., Ganesh, A., & Hill, M. D. (2018). Long-term neurological, vascular, and mortality outcomes after stroke. *International Journal of Stroke*, *13*(8), 787-796. https://doi.org/10.1177/1747493018798526

Singleton, R., & Straits, B. C. (2010). *Approaches to social research* (5th ed.). Oxford University Press.

Skriver, K., Roig, M., Lundbye-Jensen, J., Pingel, J., Helge, J. W., Kiens, B., & Nielsen, J. B. (2014). Acute exercise improves motor memory: Exploring potential biomarkers. *Neurobiology of Learning and Memory*, *116*, 46-58. https://doi.org/10.1016/j.nlm.2014.08.004

Slade, S. ., Dionne, C. ., Underwood, M., Buchbinder, R., Beck, B., Bennell, K., Brosseau, L., Costa, L., Cramp, F., Cup, E. ., Feehan, L., Ferreira, M., Forbes, S., Glasziou, P., Habets, B., Harris, S., Hay-Smith, J., Hillier, S., Hinman, R., … White, C. (2016). Consensus on Exercise Reporting Template (CERT): Modified delphi study. *Physical Therapy*, *96*(10), 1514–1524. https://doi.org/10.2522/ptj.20150668

Slattery, P., Saeri, A. K., & Bragge, P. (2020). Research co-design in health: A rapid overview of reviews. *Health Research Policy and Systems*, *18*(1), 17–17. https://doi.org/10.1186/s12961-020-0528-9

Smania, N., Gandolfi, M., Paolucci, S., Iosa, M., Ianes, P., Recchia, S., Giovanzana, C., Molteni, F., Avesani, R., Di Paolo, P., Zaccala, M., Agostini, M., Tassorelli, C., Fiaschi, A., Primon, D., Ceravolo, M. G., & Farina, S. (2012). Reduced-intensity modified constraint-induced movement therapy versus conventional therapy for upper extremity rehabilitation after stroke: A multicenter trial. *Neurorehabilitation and Neural Repair*, *26*(9), 1035-1045. https://doi.org/10.1177/1545968312446003

Smith, A. C., Saunders, D. H., & Mead, G. (2012). Cardiorespiratory fitness after stroke: A systematic review. *International Journal of Stroke*, *7*(6), 499–510. https://doi.org/10.1111/j.1747-4949.2012.00791.x

Snow, N. J., Mang, C. S., Roig, M., McDonnell, M. N., Campbell, K. L., & Boyd, L. A. (2016). The effect of an acute bout of moderate-intensity aerobic exercise on motor learning of a continuous tracking task. *PloS One*, *11*(2), e0150039-e0150039. https://doi.org/10.1371/journal.pone.0150039

Soh, S.-H., Joo, M. C., Yun, N. R., & Kim, M.-S. (2020). Randomized controlled trial of the lateral push-off skater exercise for high-intensity interval training vs conventional treadmill training. *Archives of Physical Medicine and Rehabilitation*, *101*(2), 187–195. https://doi.org/10.1016/j.apmr.2019.08.480

Stanne, T. M., Åberg, N. D., Nilsson, S., Jood, K., Blomstrand, C., Andreasson, U., Blennow, K., Zetterberg, H., Isgaard, J., Svensson, J., & Jern, C. (2016). Low circulating acute brain-derived neurotrophic factor levels are associated with poor long-term functional outcome after ischemic stroke. *Stroke*, *47*(7), 1943-1945. https://doi.org/10.1161/STROKEAHA.115.012383

Stark, B. A., Roth, G. A., Adebayo, O. M., Akbarpour, S., Aljunid, S. M., Alvis-Guzman, N., Ansar, A., Antonazzo, I. C., Ärnlöv, J., Artanti, K. D., Athar, M., Ausloos, M., Baltatu, O. C., Béjot, Y., Bijani, A., Bikbov, B., Birhanu, M. M., Brauer, M., Butt, Z. A., … Castañeda-Orjuela, C. A. (2021). Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurology*, *20*(10), 795–820. https://doi.org/10.1016/S1474-4422(21)00252-0

Stark, B. A., Roth, G. A., Adebayo, O. M., Akbarpour, S., Aljunid, S. M., Alvis-Guzman, N., Ansar, A., Antonazzo, I. C., Ärnlöv, J., Artanti, K. D., Athar, M., Ausloos, M., Baltatu, O. C., Béjot, Y., Bijani, A., Bikbov, B., Birhanu, M. M., Brauer, M., Butt, Z. A., . . . Murray, C. J. L. (2021). Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurology, 20*(10), 795-820. https://doi.org/10.1016/S1474-4422(21)00252-0

Sterne, J. A. C., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A.-W., Churchill, R., Deeks, J. J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y. K., Pigott, T. D., . . . Higgins, J. P. T. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Online)*, 355, i4919-i4919. https://doi.org/10.1136/bmj.i4919

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., . . . Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in

randomised trials. *BMJ (Online)*, 366, l4898-l4898. https://doi.org/10.1136/bmj.l4898

Stoykov, M. E., Corcos, D. M., & Madhavan, S. (2017). Movement-based priming: Clinical applications and neural mechanisms. *Journal of Motor Behavior, 49*(1), 88-97. https://doi.org/10.1080/00222895.2016.1250716

Stroke Foundation. (2020). National stroke audit: Rehabilitation services report 2020. Stroke Foundation. https://informme.org.au/media/drtlcbvp/rehab_strokeservicesreport_2020.pdf

Stroke Foundation. (2022). *Australian and New Zealand living clinical guidelines for stroke management*. Retrieved 4 May from https://app.magicapp.org/#/guideline/6659

Strong, B., Pudar, J., Thrift, A. G., Howard, V. J., Hussain, M., Carcel, C., de los Campos, G., & Reeves, M. J. (2021). Sex disparities in enrollment in recent randomized clinical trials of acute stroke: A meta-analysis. *JAMA Neurology*, *78*(6), 666–677. https://doi.org/10.1001/jamaneurol.2021.0873

Sullivan, K.J., Tilson, J. K., Duncan, P. W., Cen, S. Y., Rose, D. K., Hershberg, J., Correa, A., Gallichio, J., Mcleod, M., Moore, C., & Wu, S. S. (2011). Fugl-Meyer Assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. *Stroke*, *42*(2), 427–432. https://doi.org/10.1161/STROKEAHA.110.592766

Sun, J., Ke, Z., Yip, S. P., Hu, X.-l., Zheng, X.-x., & Tong, K.-y. (2014). Gradually increased training intensity benefits rehabilitation outcome after stroke by BDNF upregulation and stress suppression. *BioMed Research International*, *2014*, 925762-925768. https://doi.org/10.1155/2014/925762

Sungkarat, S., Boripuntakul, S., Kumfu, S., Lord, S. R., & Chattipakorn, N. (2018). Tai chi improves cognition and plasma BDNF in older adults with mild cognitive impairment: A randomized controlled trial. *Neurorehabilitation and Neural Repair*, *32*(2), 142-149. https://doi.org/10.1177/1545968317753682

Suzuki, A., Stern, Sarah A., Bozdagi, O., Huntley, George W., Walker, Ruth H., Magistretti, Pierre J., & Alberini, Cristina M. (2011). Astrocyte-neuron lactate transport is required for long-term memory formation. *Cell*, *144*(5), 810-823. https://doi.org/10.1016/j.cell.2011.02.018

Taha, M. A., Al-Maqati, T. N., Alnaam, Y. A., Alharbi, S. S., Khaneen, R., Almutairi, H., & Al-Harbi, M. (2022). The Association between Brain-Derived Neurotrophic Factor (BDNF) protein level and body mass index. *Medicina (Kaunas, Lithuania)*, *59*(1), 99–. https://doi.org/10.3390/medicina59010099

Tang, A., Sibley, K. M., Thomas, S. G., Bayley, M. T., Richardson, D., McIlroy, W. E., & Brooks, D. (2009). Effects of an aerobic exercise program on aerobic capacity, spatiotemporal gait parameters, and functional capacity in subacute stroke. *Neurorehabilitation and Neural Repair*, *23*(4), 398-406. https://doi.org/10.1177/1545968308326426

Taub, E., Crago, J. E., Burgio, L. D., Groomes, T. E., Cook III, E. W., DeLuca, S. C., & Miller, N. E. (1994). An operant approach to rehabilitation medicine: overcoming learned nonuse by shaping. *Journal of the Experimental Analysis of Behavior*, *61*(2), 281–293. https://doi.org/10.1901/jeab.1994.61-281

Taub, E., McCulloch, K., Uswatte, G. & Morris, D. M. (2011). Motor activity log (MAL) manual. Retrieved from https://www.uab.edu/citherapy/images/pdf_files/CIT_Training_MAL_manual.pdf.

Taub, E., Miller, N. E., Novack, T. A., Cook, E. W., Fleming, W. C., Nepomuceno, C. S., Connell, J. S., & Crago, J. E. (1993). Technique to improve chronic motor deficit after stroke. *Archives of Physical Medicine and Rehabilitation*, *74*(4), 347-354.

Taub, E., Uswatte, G., Mark, V. W., & Morris, D. M. (2006). The learned nonuse phenomenon: Implications for rehabilitation. *Europa Medicophysica*, *42*(3), 241-255.

Taub, E., Uswatte, G., Mark, V. W., Morris, D. M., Barman, J., Bowman, M. H., Bryson, C., Delgado, A., & Bishop-Mckay, S. (2013). Method for enhancing real-world use of a more affected arm in chronic stroke transfer package of constraint-induced movement therapy. *Stroke*, *44*(5), 1383-1388. https://doi.org/10.1161/STROKEAHA.111.000559

Taubert, M., Villringer, A., & Lehmann, N. (2015). Endurance exercise as an “endogenous” neuro-enhancement strategy to facilitate motor learning. *Frontiers in Human Neuroscience*, *9*, 692–692. https://doi.org/10.3389/fnhum.2015.00692

Taylor, J. L., Holland, D. J., Spathis, J. G., Beetham, K. S., Wisløff, U., Keating, S. E., & Coombes, J. S. (2019). Guidelines for the delivery and monitoring of high intensity interval training in clinical populations. *Progress in Cardiovascular Diseases*, *62*(2), 140–146. https://doi.org/10.1016/j.pcad.2019.01.004

Teasell, R., Hussein, N., Mirkowski, M., Vanderlaan, D., Saikaley, M., Longval, M., & Iruthayarajah, J. (2020). Hemiplegic upper extremity rehabilitation. In *Stroke Rehabilitation Clinician Handbook* (pp. 1-60). Heart & Stroke Foundation Canadian Partnership for Stroke Recovery. http://www.ebrsr.com/sites/default/files/EBRSR%20Handbook%20Chapter%204_Upper%20Extremity%20Post%20Stroke_ML.pdf

Thomas, R., Flindtgaard, M., Skriver, K., Geertsen, S. S., Christiansen, L., Korsgaard Johnsen, L., Busk, D. V. P., Bojsen-Møller, E., Madsen, M. J., Ritz, C., Roig, M., & Lundbye-Jensen, J. (2017). Acute exercise and motor memory consolidation: Does exercise type play a role? *Scandinavian Journal of Medicine and Science in Sports*, *27*(11), 1523-1532. https://doi.org/10.1111/sms.12791

Thomas, R., Johnsen, L. K., Geertsen, S. S., Christiansen, L., Ritz, C., Roig, M., & Lundbye-Jensen, J. (2016). Acute exercise and motor memory consolidation: The role of exercise intensity. *PloS One*, *11*(7), e0159589-e0159589. https://doi.org/10.1371/journal.pone.0159589

Tiozzo, E., Youbi, M., Dave, K., Perez-Pinzon, M., Rundek, T., Sacco, R. L., Loewenstein, D., Lewis, J. E., & Wright, C. B. (2015). Aerobic, resistance, and cognitive exercise training poststroke. *Stroke*, *46*(7), 2012-2016. https://doi.org/10.1161/STROKEAHA.114.006649

Tomita, Y., Rodrigues, M. R. M., & Levin, M. F. (2017). Upper limb coordination in individuals with stroke: Poorly defined and poorly quantified. *Neurorehabilitation and Neural Repair*, *31*(10-11), 885-897. https://doi.org/10.1177/1545968317739998

Tschakert, G., & Hofmann, P. (2013). High-intensity intermittent exercise: methodological and physiological aspects. *International Journal of Sports Physiology and Performance, 8*(6), 600–610. https://doi.org/10.1123/ijspp.8.6.600

Tsukamoto, H., Suga, T., Takenaka, S., Tanaka, D., Takeuchi, T., Hamaoka, T., Isaka, T., & Hashimoto, T. (2015). Greater impact of acute high-intensity interval exercise on post-exercise executive function compared to moderate-intensity continuous exercise. *Physiology and Behavior*, *155*, 224-230. https://doi.org/10.1016/j.physbeh.2015.12.021

Tsukamoto, H., Suga, T., Takenaka, S., Tanaka, D., Takeuchi, T., Hamaoka, T., Isaka, T., Ogoh, S., & Hashimoto, T. (2016). Repeated high-intensity interval exercise shortens the

positive effect on executive function during post-exercise recovery in healthy young males. *Physiology and Behavior*, *160*, 26-34. https://doi.org/10.1016/j.physbeh.2016.03.029

Turan, T. N., Nizam, A., Lynn, M. J., Egan, B. M., Le, N.-A., Lopes-Virella, M. F., Hermayer, K. L., Harrell, J., Derdeyn, C. P., Fiorella, D., Janis, L. S., Lane, B., Montgomery, J., & Chimowitz, M. I. (2017). Relationship between risk factor control and vascular events in the SAMMPRIS trial. *Neurology*, *88*(4), 379-385. https://doi.org/10.1212/WNL.0000000000003534

Upadhaya, S., Yu, J. X., Oliva, C., Hooton, M., Hodge, J., & Hubbard-Lucey, V. M. (2020). Impact of COVID-19 on oncology clinical trials. *Nature Reviews. Drug Discovery*, *19*(6), 376–377. https://doi.org/10.1038/d41573-020-00093-1

Uswatte, G., Taub, E., Morris, D., Light, K., & Thompson, P. A. (2006). The motor activity log-28: Assessing daily use of the hemiparetic arm after stroke. *Neurology*, *67*(7), 1189-1194. https://doi.org/10.1212/01.wnl.0000238164.90657.c2

Uswatte, G., Taub, E., Morris, D., Vignolo, M., & Mcculloch, K. (2005). Reliability and validity of the upper-extremity motor activity log-14 for measuring real-world arm use. *Stroke, 36*(11), 2493–2496.

Valkenborghs, S. R., Vliet, P., Nilsson, M., Zalewska, K., Visser, M. M., Erickson, K. I., & Callister, R. (2019). Aerobic exercise and consecutive task-specific training (AExaCTT) for upper limb recovery after stroke: A randomized controlled pilot study. *Physiotherapy Research International*, *24*(3), e1775-n/a. https://doi.org/10.1002/pri.1775

van der Lee, J. H., Beckerman, H., Knol, D. L., de Vet, H. C. W., & Bouter, L. M. (2004). Clinimetric properties of the motor activity log for the assessment of arm use in hemiparetic patients. *Stroke, 35*(6), 1410–1414. https://doi.org/10.1161/01.STR.0000126900.24964.7e

van Dongen, E. V., Kersten, I. H. P., Wagner, I. C., Morris, R. G. M., & Fernandez, G. (2016). Physical exercise performed four hours after learning improves memory retention and increases hippocampal pattern similarity during retrieval. *Current Biology*, *26*(13), 1722-1727. https://doi.org/10.1016/j.cub.2016.04.071

van Hall, G. (2010). Lactate kinetics in human tissues at rest and during exercise. *Acta Physiologica, 199*(4), 499–508. https://doi.org/10.1111/j.1748-1716.2010.02122.x

van Uffelen, J. G. Z., Chin A Paw, M. J. M., Hopman-Rock, M., & van Mechelen, W. (2008). The effects of exercise on cognition in older adults with and without cognitive decline: A systematic review. *Clinical Journal of Sport Medicine*, *18*(6), 486-500. https://doi.org/10.1097/JSM.0b013e3181845f0b

Veldsman, M., Cumming, T., & Brodtmann, A. (2015). Beyond BOLD: Optimizing functional imaging in stroke populations. *Human Brain Mapping*, *36*(4), 1620–1636. https://doi.org/10.1002/hbm.22711

Viktorisson, A., Andersson, E. M., Lundström, E., & Sunnerhagen, K. S. (2021). Levels of physical activity before and after stroke in relation to early cognitive function. *Scientific Reports, 11*(1), 9078-9078. https://doi.org/10.1038/s41598-021-88606-9

Voss, P., Thomas, M. E., Cisneros-Franco, J. M., & de Villers-Sidani, É. (2017). Dynamic brains and the changing rules of neuroplasticity: Implications for learning and recovery. *Frontiers in Psychology*, *8*, 1657-1657. https://doi.org/10.3389/fpsyg.2017.01657

Walker, M. F., Hoffmann, T. C., Brady, M. C., Dean, C. M., Eng, J. J., Farrin, A. J., Felix, C., Forster, A., Langhorne, P., Lynch, E. A., Radford, K. A., Sunnerhagen, K. S., & Watkins, C. L. (2017). Improving the development, monitoring and reporting of stroke rehabilitation research: Consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. *Neurorehabilitation and Neural Repair, 31*(10-11), 877.

Walsh, E. I., Smith, L., Northey, J., Rattray, B., & Cherbuin, N. (2020). Towards an understanding of the physical activity-BDNF-cognition triumvirate: A review of associations and dosage. *Ageing Research Reviews*, *60*, 101044-101044. https://doi.org/10.1016/j.arr.2020.101044

Wang, J., Gao, L., Yang, Y.-L., Li, Y.-Q., Chang, T., Man, M.-H., Zhang, X.-Y., Guo, S.-C., & Li, L.-H. (2017). Low serum levels of brain-derived neurotrophic factor were associated with poor short-term functional outcome and mortality in acute ischemic stroke. *Molecular Neurobiology*, *54*(9), 7335-7342. https://doi.org/10.1007/s12035-016-0236-1

Wang, J., Huang, Q., Ding, J., & Wang, X. (2019). Elevated serum levels of brain-derived neurotrophic factor and miR-124 in acute ischemic stroke patients and the molecular mechanism. *3 Biotech*, *9*(11), 1-6. https://doi.org/10.1007/s13205-019-1914-2

Wang, Z.-H., Xiang, J., Liu, X., Yu, S. P., Manfredsson, F. P., Sandoval, I. M., Wu, S., Wang, J.-Z., & Ye, K. (2019). Deficiency in BDNF/TrkB neurotrophic activity stimulates δ-secretase by upregulating C/EBPβ in Alzheimer's Disease. *Cell Reports, 28*(3), 655-669.e5. https://doi.org/10.1016/j.celrep.2019.06.054

Wang, Q., Zhao, J.-L., Zhu, Q.-X., Li, J., & Meng, P.-P. (2011). Comparison of conventional therapy, intensive therapy and modified constraint-induced movement therapy to improve upper extremity function after stroke. *Journal of Rehabilitation Medicine*, *43*(7), 619-625. https://doi.org/10.2340/16501977-0819

Ward, N. S., Brown, M. M., Thompson, A. J., & Frackowiak, R. S. J. (2003). Neural correlates of motor recovery after stroke: A longitudinal fMRI study. *Brain*, *126*(11), 2476-2496. https://doi.org/10.1093/brain/awg245

Wei, Y. C., Wang, S. R., & Xu, X. H. (2017). Sex differences in brain-derived neurotrophic factor signaling: Functions and implications. *Journal of Neuroscience Research*, *95*(1-2), 336–344. https://doi.org/10.1002/jnr.23897

Weinstein, G., Beiser, A. S., Choi, S. H., Preis, S. R., Chen, T. C., Vorgas, D., Au, R., Pikula, A., Wolf, P. A., DeStefano, A. L., Vasa, R. S., & Seshadri, S. (2014). Serum brain-derived neurotrophic factor and the risk for dementia: The Framingham Heart Study. *JAMA Neurology, 71*(1), 55-61. https://doi.org/10.1001/jamaneurol.2013.4781

Wieloch, T., & Nikolich, K. (2006). Mechanisms of neural plasticity following brain injury. *Current Opinion in Neurobiology*, *16*(3), 258-264. https://doi.org/10.1016/j.conb.2006.05.011

Wiener, J., McIntyre, A., Janssen, S., Chow, J. T., Batey, C., & Teasell, R. (2019). Effectiveness of high-intensity interval training for fitness and mobility post stroke: A systematic review. *Physical Medicine & Rehabiltiation*, *11*(8), 868–878. https://doi.org/10.1002/pmrj.12154

Wilson, R. C., & Jones, P. W. (1989). A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. *Clinical Science*, *76*(3), 277–282. https://doi.org/10.1042/cs0760277

Wisløff, U., Støylen, A., Videm, V., Bye, A., Smith, G. L., Najjar, S. M., Ellingsen, Ø., Skjaerpe, T., Loennechen, J. P., Bruvold, M., Rognmo, Ø., Haram, P. M., Tjønna, A. E., Helgerud, J., Slørdahl, S. A., & Sang Jun Lee. (2007). Superior cardiovascular effect of aerobic

interval training versus moderate continuous training in heart failure patients : A randomized study. *Circulation, 115*(24), 3086–3094. https://doi.org/10.1161/CIRCULATIONAHA.106.675041

Wlodarczyk, L., Szelenberger, R., Cichon, N., Saluk-Bijak, J., Bijak, M., & Miller, E. (2021). Biomarkers of angiogenesis and neuroplasticity as promising clinical tools for stroke recovery evaluation. *International Journal of Molecular Sciences*, *22*(8), 3949. https://doi.org/10.3390/ijms22083949

Wolf, S. L., Catlin, P. A., Ellis, M., Archer, A. L., Morgan, B., & Piacentino, A. (2001). Assessing Wolf Motor Function Test as outcome measure for research in patients after stroke. *Stroke*, *32*(7), 1635-1639. https://doi.org/10.1161/01.STR.32.7.1635

Wolf, S. L., Winstein, C. J., Miller, J. P., Taub, E., Uswatte, G., Morris, D., Giuliani, C., Light, K. E., Nichols-Larsen, D., & EXCITE Investigators. (2006). Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE randomized clinical trial. *JAMA: The Journal of the American Medical Association, 296*(17), 2095–2104. https://doi.org/10.1001/jama.296.17.2095

Wrann, C. D., White, J. P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Lin, J. D., Greenberg, M. E., & Spiegelman, B. M. (2013). Exercise induces hippocampal BDNF through a PGC-1a/FNDC5 pathway. *Cell Metabolism*, *18*(5), 649-659. https://doi.org/10.1016/j.cmet.2013.09.008

Wu, C.-y., Lin, K.-c., Chen, H.-c., Chen, I. h., & Hong, W.-h. (2007). Effects of modified constraint-induced movement therapy on movement kinematics and daily function in patients with stroke: A kinematic study of motor control mechanisms. *Neurorehabilitation and Neural Repair*, *21*(5), 460-466. https://doi.org/10.1177/1545968307303411

Wu, C.-y., Yang, C.-l., Chuang, L.-l., Lin, K.-c., Chen, H.-c., Chen, M.-d., & Huang, W.-c. (2012). Effect of therapist-based versus robot-assisted bilateral arm training on motor control, functional performance, and quality of life after chronic stroke: A clinical trial. *Physical Therapy*, *92*(8), 1006-1016. https://doi.org/10.2522/ptj.20110282

Wyss, M. T., Jolivet, R., Buck, A., Magistretti, P. J., & Weber, B. (2011). In Vivo evidence for lactate as a neuronal energy source. *The Journal of Neuroscience*, *31*(20), 7477–7485. https://doi.org/10.1523/JNEUROSCI.0415-11.2011

Xu, A.-H., & Sun, Y.-X. (2020). Research hotspots and effectiveness of repetitive transcranial magnetic stimulation in stroke rehabilitation. *Neural Regeneration Research*, *15*(11), 2089–2097. https://doi.org/10.4103/1673-5374.282269

Yamamoto, H., Takeda, K., Koyama, S., Morishima, K., Hirakawa, Y., Motoya, I., Sakurai, H., Kanada, Y., Kawamura, N., Kawamura, M., & Tanabe, S. (2020). Relationship between upper limb motor function and activities of daily living after removing the influence of lower limb motor function in subacute patients with stroke: A cross-sectional study. *Hong Kong Journal of Occupational Therapy*, *33*(1), 12-17. https://doi.org/10.1177/1569186120926609

Yarrow, J. F., White, L. J., McCoy, S. C., & Borst, S. E. (2010). Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). *Neuroscience Letters*, *479*(2), 161-165. https://doi.org/10.1016/j.neulet.2010.05.058

Yates, J. S., Studenski, S., Gollub, S., Whitman, R., Perera, S., Lai, S. M., & Duncan, P. W. (2004). Bicycle ergometry in subacute-stroke survivors: feasibility, safety, and exercise performance. *Journal of Aging and Physical Activity*, *12*(1), 64-74. https://doi.org/10.1123/japa.12.1.64

Yilmazer, C., Boccuni, L., Thijs, L., & Verheyden, G. (2019). Effectiveness of somatosensory interventions on somatosensory, motor and functional outcomes in the upper limb post-stroke: A systematic review and meta-analysis. *NeuroRehabilitation*, *44*(4), 459-477. https://doi.org/10.3233/NRE-192687

Yozbatiran, N., Der-Yeghiaian, L., & Cramer, S. C. (2008). A standardized approach to performing the action research arm test. *Neurorehabilitation and Neural Repair*, *22*(1), 78-90. https://doi.org/10.1177/1545968307305353

Yu, C., Wang, W., Zhang, Y., Wang, Y., Hou, W., Liu, S., Gao, C., Wang, C., Mo, L., & Wu, J. (2017). The effects of modified constraint-induced movement therapy in acute subcortical cerebral infarction. *Frontiers in Human Neuroscience*, *11*, 265-265. https://doi.org/10.3389/fnhum.2017.00265

Zenke, F., Agnes, E. J., & Gerstner, W. (2015). Diverse synaptic plasticity mechanisms orchestrated to form and retrieve memories in spiking neural networks. *Nature Communications*, *6*, 6922–. https://doi.org/10.1038/ncomms7922

Zhang, Y., Huang, L., Wang, D., Ren, P., Hong, Q., & Kang, D. (2021). The ROBINS-I and the NOS had similar reliability but differed in applicability: A random sampling

observational studies of systematic reviews/meta-analysis. *Journal of Evidence-Based Medicine, 14*(2), 112-122. https://doi.org/10.1111/jebm.12427

Ziegenhorn, A. A., Schulte-Herbrüggen, O., Danker-Hopfe, H., Malbranc, M., Hartung, H.-D., Anders, D., Lang, U. E., Steinhagen-Thiessen, E., Schaub, R. T., & Hellweg, R. (2007). Serum neurotrophins—A study on the time course and influencing factors in a large old age sample. *Neurobiology of Aging*, *28*(9), 1436–1445. https://doi.org/10.1016/j.neurobiolaging.2006.06.011

Zlowodzki, M., Poolman, R. W., Kerkhoffs, G. M., Tornetta, P., Bhandari, M., & On behalf of the International Evidence-Based Orthopedic Surgery Working, G. (2007). How to interpret a meta-analysis and judge its value as a guide for clinical practice. *Acta Orthopaedica, 78*(5), 598-609. https://doi.org/10.1080/17453670710014284

Chapter 12 Appendices

12.1 Appendix 1: People with stroke questionnaire (as downloaded from REDCap)

Questionnaire

Thank you for participating in this questionnaire looking at your opinions on High Intensity Interval Training (HIIT) after your stroke.

This questionnaire has six sections and should take you approximately 10 minutes to complete.

If you find any of these questions hard or upsetting, please feel free to stop the questionnaire. You can always come back to it later if you like.

Section 1. Background Information **This section will ask you questions about yourself, your stroke and how you function on a day-to-day basis.**	
What is your age?	◯ 18 - 29 ◯ 30 - 39 ◯ 40 - 49 ◯ 50 - 59 ◯ 60 - 69 ◯ 70 - 79 ◯ 80 - 89 ◯ 90 - 99 ◯ 100+
What is your sex?	◯ Male ◯ Female ◯ Other ◯ Would prefer not to say
When was your most recent stroke? Please provide the year and month if you know it.	_____
Do you identify as Aboriginal and/or Torres Strait Islander?	◯ Yes ◯ No ◯ Prefer not to say
Do you experience any difficulty in the following areas since your stroke? Please tick all that apply.	☐ Walking ability ☐ Arm use ☐ Memory ☐ Communication ☐ Fatigue ☐ I do not experience any difficulties since my stroke
Since your stroke, have you started using a walking aid?	◯ When I walk inside and outside ◯ Only when I walk outside ◯ Only when I walk long distances ◯ Never
What type of walking aid do you use? Please tick all that apply.	☐ Cane/ Walking stick/ Quad stick ☐ Crutches ☐ Walker ☐ Wheelchair ☐ Foot orthoses

Section 2. Exercise BEFORE Stroke

This section will ask you questions about your exercise habits before your stroke.

Exercise is defined as any structured, repetitive, and/or planned body movement that you complete for the goal of improving your health and movement ability.

Did you enjoy exercise before your stroke?	◯ Yes ◯ No ◯ Sometimes ◯ I did not exercise before my stroke
What type(s) of exercise did you regularly complete before your stroke? Please tick all that apply. Regularly refers to exercise that you completed as part of your usual exercise routine.	☐ Heart health exercise (e.g., walking, jogging/running, cycling, swimming, dancing, boxing) ☐ Yoga/ Tai Chi/ Pilates ☐ Muscle strength training (e.g., bodyweight, hand-held weights, machines) ☐ Balance exercises ☐ Sport and recreation
Are there any other type(s) of exercise you regularly completed before your stroke?	_____
On average, how many days per week did you exercise before your stroke?	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7
On average, how long did you exercise for in each of your exercise sessions before your stroke?	◯ Less than 30 minutes ◯ 30 - 60 minutes ◯ More than 60 minutes
How much effort did you feel it took to complete your regular exercise before your stroke?	◯ Easy (could speak in full sentences) ◯ Moderate (deeper breathing and talking was a bit more difficult) ◯ Hard (deep forced breathing, could not really talk) ◯ Combination of easy and moderate ◯ Combination of moderate and hard ◯ Combination of easy and hard

Section 3. Exercise AFTER Stroke

This section will ask you questions about your exercise habits after your stroke.

Exercise is defined as any structured, repetitive, and/or planned body movement that you complete for the goal of improving your health and movement ability.

Do you enjoy doing exercise since your stroke?	◯ Yes ◯ No ◯ Sometimes
What do you think is your main reason for doing exercise of any kind after your stroke?	◯ To help my health ◯ To prevent another stroke ◯ To move around better ◯ I was told to exercise after my stroke ◯ I do not exercise ◯ Other
What is your main reason for doing exercise after your stroke?	_____
What type(s) of exercise do you regularly complete since having your stroke? Please tick all that apply. Regularly refers to exercise that you completed as part of your usual exercise routine.	☐ Heart health exercise (e.g., walking, jogging/running, cycling, swimming, dancing, boxing) ☐ Yoga/ Tai Chi/ Pilates ☐ Muscle strength training (e.g., bodyweight, hand-held weights, machines) ☐ Balance exercises ☐ Sport and recreation
Are there any other type(s) of exercise you regularly complete since having your stroke?	_____
On average, how many days per week do you complete exercise since having your stroke?	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7
On average, how long do you exercise for in your exercise sessions since having your stroke?	◯ Less than 30 minutes ◯ 30 - 60 minutes ◯ More than 60 minutes
How much effort do you feel it takes to complete your regular exercise since having your stroke?	◯ Easy (could speak in full sentences) ◯ Moderate (deeper breathing and talking was a bit more difficult) ◯ Hard (deep forced breathing, could not really talk) ◯ Combination of easy and moderate ◯ Combination of moderate and hard ◯ Combination of easy and hard

Section 4. High Intensity Interval Training (HIIT)

This section will ask you questions about whether you have done HIIT and if you would be interested in doing HIIT in the future.

HIIT sessions:

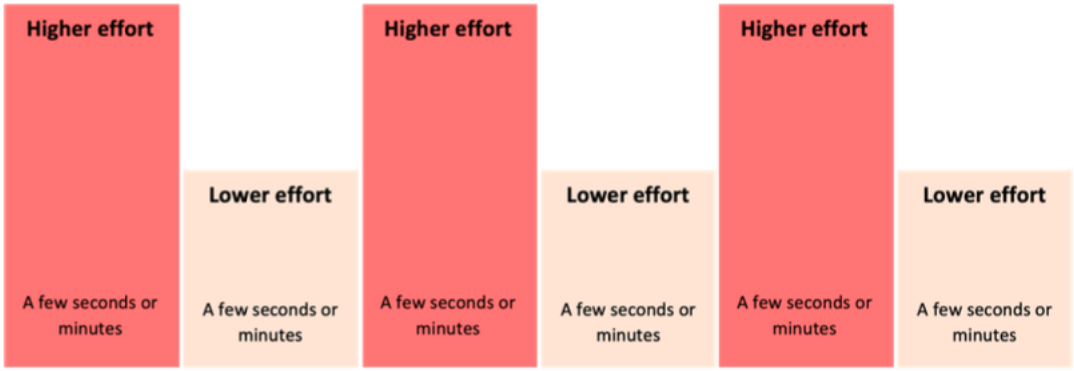
- Are a form of heart health exercise involving alternating brief bouts of higher effort exercise and lighter effort exercise.

- In total, can last from just a few minutes up to about 30 minutes.

- Are individualised to your fitness and interests.

- Can be done on a bike (legs or arms), treadmill, boxing and many more ways.

The following graphic represents a common approach to a HIIT session:



Have you ever done HIIT?	◯ Yes ◯ No ◯ I am not sure
Would you be interested in doing HIIT after your stroke?	◯ Yes ◯ No ◯ Maybe

Section 5. Concerns about HIIT after Stroke

This section will ask you questions about your concerns about doing HIIT after your stroke.

Just a reminder, HIIT is a form of heart health exercise involving alternating brief bouts of higher effort exercise and lighter effort exercise.

Please rate your level of agreement with each of the following statements about what might stop you from participating in HIIT since having your stroke. Please only tick one response per line.

	Strongly Agree	Agree	Maybe	Disagree	Strongly Disagree
My fear of making my health worse would stop me from doing HIIT	○	○	○	○	○
My fear of falling would stop me from doing HIIT	○	○	○	○	○
Pain would stop me from doing HIIT	○	○	○	○	○
HIIT sounds too hard	○	○	○	○	○
I am not motivated enough to do HIIT	○	○	○	○	○
I would feel uncomfortable or embarrassed when doing HIIT	○	○	○	○	○
My fatigue would stop me from doing HIIT	○	○	○	○	○
I think my stroke impairments would stop me from doing HIIT	○	○	○	○	○
I do not want to do HIIT because it is not my top priority after my stoke	○	○	○	○	○
I do not have enough time to do regular HIIT sessions	○	○	○	○	○
I do not have access to a place to do HIIT (e.g., space at home, park, gym)	○	○	○	○	○
I do not have the equipment needed to do HIIT	○	○	○	○	○
I would not do HIIT because I don't have an exercise professional to supervise me	○	○	○	○	○

I would not do HIIT because I don't know enough about HIIT	○	○	○	○	○
I do not know the benefits of HIIT after stroke	○	○	○	○	○
No health professional has ever spoken to me about doing HIIT after my stroke	○	○	○	○	○
My family or friends do not want me to do HIIT	○	○	○	○	○
I do not know anyone who has done HIIT after their stroke	○	○	○	○	○

Are there any other reasons that may stop you from doing HIIT since having your stroke that are not on this list? If so, please describe them. _____

Section 6. Motivators for HIIT after Stroke

This section will ask you questions about your motivators for HIIT after your stroke.

Just a reminder, HIIT is a form of heart health exercise involving alternating brief bouts of higher effort exercise and lighter effort exercise.

Please rate your level of agreement with each of the following statements about what might motivate you to participate in HIIT since having your stroke. Please only tick one response per line.

	Strongly Agree	Agree	Maybe	Disagree	Strongly Disagree
I would do HIIT if a trained professional was supervising me	○	○	○	○	○
I would do HIIT if it was safe for me to do so	○	○	○	○	○
I would do HIIT if it meant I could meet more people who have had a stroke	○	○	○	○	○
I would do HIIT if my family and/or friends could be involved	○	○	○	○	○
I would do HIIT to get better (mentally and physically) after my stroke	○	○	○	○	○
I would do HIIT to help me get back to my pre-stroke activities	○	○	○	○	○
I would do HIIT to help improve my recovery after stroke	○	○	○	○	○
I would do HIIT if it was tailored to my fitness level and abilities	○	○	○	○	○
I would do HIIT if I was able to do it from home	○	○	○	○	○
I would do HIIT if I was able to do it via telehealth/video conferencing (e.g., Zoom)	○	○	○	○	○
I would do HIIT if the sessions were shorter/fit my schedule	○	○	○	○	○

Are there any other reasons that may motivate you to do HIIT after your stroke that are not on this list?
If so, please describe them. _____

12.2 Appendix 2: Health professional questionnaire (as downloaded from REDCap)

Questionnaire

Thank you for participating in this study looking at your opinions on High Intensity Interval Training (HIIT) after stroke.

This questionnaire has five sections and should take you approximately 10 minutes to complete.

If you find any of these questions hard or upsetting, please feel free to stop the questionnaire. You can always come back to it later if you like.

Section 1. Background Information **This section will ask you questions about yourself, your professional experience with people with stroke and the colleagues you work with.**	
What is your health profession?	◯ Allied Health Assistant ◯ Cardiologist ◯ Endocrinologist ◯ Exercise Physiologist ◯ General Practitioner ◯ Neurologist ◯ Physiotherapist ◯ Rehabilitation Physician ◯ Other
What is the title of your health profession?	_____
What is your highest level of education relevant to your current health profession?	◯ Certificate ◯ Bachelors degree ◯ Graduate diploma ◯ Masters degree ◯ Doctorate
How many years of experience do you have in your current health professional position working with people with stroke?	◯ < 1 year ◯ 1 - 5 years ◯ 5 - 10 years ◯ >10 years
In what phase of recovery are the people with stroke you work with? Please tick all that apply.	☐ Hyperacute (0 - 24 hours) ☐ Acute (1 - 7 days) ☐ Early subacute (7 days - 3 months) ☐ Late subacute (3 - 6 months) ☐ Chronic (>6 months)
What is your employment setting when working with people with stroke? Please tick all that apply.	☐ Inpatient hospital ☐ Hospital outpatient clinic ☐ Community outpatient clinic ☐ Inpatient rehabilitation hospital ☐ Mobile service/ Home rehabilitation ☐ Academic/research centre ☐ Aged care centre
If your employment setting when working with people with stroke was not on the above list, please describe your employment setting.	_____

Do you work as part of a multidisciplinary team when working with people with stroke?	◯ Yes ◯ No ◯ Sometimes
What other health professionals are part of your multidisciplinary team when working with people with stroke? Please tick all that apply.	☐ Allied Health Assistant ☐ Cardiologist ☐ Endocrinologist ☐ Exercise Physiologist ☐ General Practitioner ☐ Neurologist ☐ Nurse ☐ Occupational Therapist ☐ Physiotherapist ☐ Rehabilitation Physician ☐ Social Worker ☐ Specialist
Are there any other health professionals are part of your multidisciplinary team when working with people with stroke that were not on the above list?	_____

Section 2. Aerobic Exercise AFTER Stroke

This section will ask you questions about your opinions on exercise for people with stroke.

Exercise refers to any structured, repetitive, and/or planned movement completed for the purpose of improving health and movement ability.

Aerobic exercise refers to exercise aimed at increasing cardiorespiratory fitness (e.g., walking, running, cycling).

Does part of your role include recommending/prescribing aerobic exercise to people with stroke?

- ◯ Yes
- ◯ No

Please rate your level of agreement with each of the following statements about exercise for people with stroke? Please only tick one response per statement.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
People with stroke should be prescribed aerobic exercise training as part of rehabilitation	◯	◯	◯	◯	◯
People with stroke should receive education on the importance of lifelong exercise and physical activity after stroke	◯	◯	◯	◯	◯
People with stroke should be referred to a qualified exercise professional (i.e. Exercise Physiologist, Physiotherapist)	◯	◯	◯	◯	◯

Section 3. High Intensity Interval Training (HIIT)

This section will ask you about your opinions, and use, of HIIT.

HIIT sessions:

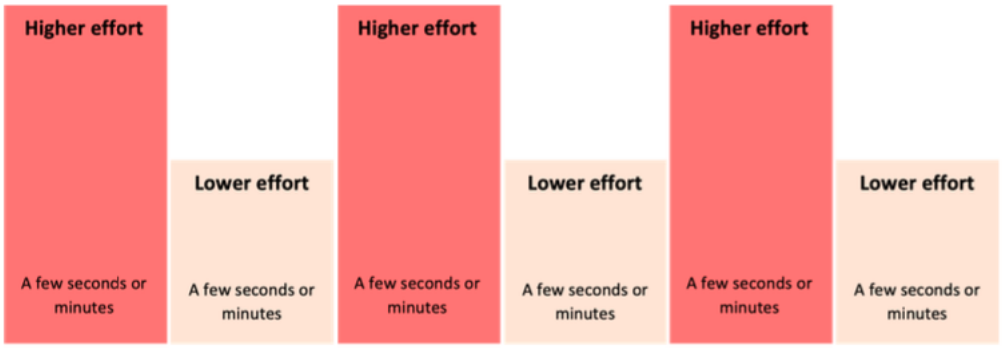
- Are a form of aerobic exercise involving alternating brief bouts of higher effort exercise and lighter effort exercise.

- In total, can last from just a few minutes up to about 30 minutes.

- Are individualised to your patients/clients fitness and interests.

- Can be done on a bike (legs or arms), treadmill, boxing and many more ways.

The following graphic represents a common approach to HIIT:



Do you ever recommend or prescribe HIIT to people with stroke?

- ◯ Yes
- ◯ No
- ◯ Exercise prescription is not part of my role

Section 4. Barriers to Recommending/Prescribing HIIT after Stroke

This section will ask you about your opinons on potential barriers to the recommendation and/or prescription of HIIT to people with stroke.

Do you feel confident in recommending or prescribing HIIT to people with stroke?

- ○ Yes
- ○ No

Please rate your level of agreement with each of the following statements about what may prevent/limit you from recommending or prescribing HIIT to people with stroke. Please tick only one response per statement.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I am qualified to recommend/prescribe HIIT to people with stroke	○	○	○	○	○
I do not know how to prescribe HIIT to people with stroke	○	○	○	○	○
I am unsure how HIIT should be tailored for varying degrees of post-stroke physical and/or neurological impairments	○	○	○	○	○
I am unsure of how long after stroke it is safe to commence HIIT	○	○	○	○	○
I do not know the benefits of HIIT for people with stroke	○	○	○	○	○
The benefits of HIIT do not outweigh the potential risks (e.g., falls, injury, recurrent stroke) of HIIT for people with stroke	○	○	○	○	○
I cannot safely provide HIIT to people with stroke in my professional setting	○	○	○	○	○
I don't have the resources I need to prescribe HIIT to people with stroke in my professional setting	○	○	○	○	○
I do not have enough time to recommend/prescribe HIIT to people with stroke	○	○	○	○	○
HIIT should not be a top rehabilitation priority for people with stroke	○	○	○	○	○
The age of people with stroke may stop me recommending/ prescribing HIIT to them	○	○	○	○	○

A reduced motivation to exercise by people with stroke stops me recommending/prescribing HIIT	○	○	○	○	○
The fatigue levels of people with stroke stops me recommending/prescribing HIIT	○	○	○	○	○
Low levels of pre-stroke exercise by the people with stroke stops me recommending/prescribing HIIT	○	○	○	○	○
A lack of encouragement from the partner, family or friends of people with stroke stops me recommending/prescribing HIIT to people with stroke	○	○	○	○	○
I am not supported by other members of the people with stroke's healthcare team to recommend/prescribe HIIT	○	○	○	○	○

Are there any other reasons that may stop you from recommending and/or prescribing HIIT to people with stroke that are not on this list? If so, please describe them.

_____

Section 5. Facilitators to Recommending/Prescribing HIIT after Stroke

This section will ask you questions about your opinions on potential facilitators to the recommendation and/or prescription of HIIT to people with stroke.

Have you ever received formal training on how to recommend/prescribe HIIT to people with stroke?	◯ Yes ◯ No
Where did you primarily receive this training?	◯ University degree ◯ Graduate certificate ◯ Professional development course ◯ Taught by a senior clinician within the workplace ◯ Self-taught ◯ Other
Where did you receive your training on how to recommend/prescribe HIIT to people with stroke?	_____

Please rate your level of agreement with each of the following statements about what may help you in recommending and/or prescribing HIIT to people with stroke. Please only tick one response per statement.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I am interested and willing to learn or improve the knowledge I need to incorporate HIIT into routine stroke care	◯	◯	◯	◯	◯
One-on-one supervised sessions with an exercise professional would facilitate safer HIIT prescriptions for people with stroke	◯	◯	◯	◯	◯
Group HIIT classes would be more engaging for people with stroke	◯	◯	◯	◯	◯
Telehealth HIIT sessions could be made safe for people with stroke with appropriate screening, pre-exercise site-visits and safety monitoring	◯	◯	◯	◯	◯
Medical clearance from a doctor to participate in HIIT is necessary before a person with stroke commences HIIT	◯	◯	◯	◯	◯

12.3 Appendix 3: People with stroke semi-structured interview script

Good morning/afternoon and welcome. My name is Sarah Ashcroft, and I am a researcher with Australian Catholic University. Thank you again for agreeing to talk with me today.

This interview is part of a research project investigating the benefits of exercise after stroke. In particular, we have found that High Intensity Interval Training (HIIT), which is a form of heart exercise involving small amounts of high effort exercise broken up with small amounts of lighter effort exercise in between, has shown great benefits for the heart, muscles, and brain after stroke. However, we are not sure what may be stopping stroke survivors from participating in HIIT exercise, or what may help to motivate them to participate in HIIT. We hope to use this information to teach health professionals of ways to improve their therapy programs to ensure stroke survivors are enjoying therapy and receiving the best benefits exercise can provide.

To help with this, my research team and I are interested in understanding your experience with exercise after stroke as well as your opinions on what strategies might increase your participation in exercise in the future.

In particular, there are a few different topics I would like to discuss with you:

- Your current exercise routine.
- What helps you to get your exercise done, as well as what might get in the way of you being able to do exercise.
- And finally, your thoughts on High Intensity Interval Training, or HIIT, which is a particular type of aerobic exercise which involves brief bouts of alternating higher and lower intensity exercise.

This discussion is confidential – while we hope to present this information to researchers and health professionals, your name will not be used publicly so please do not hesitate to share your point of view. There are no right or wrong answers. We are recording the session, but the recordings will not be shared to anyone outside of the research team. If at any time you don't feel comfortable sharing your opinions or do not want to participate any further, you are free to not respond or withdraw at any time. Also, if any topics are uncomfortable for you, do let me know and we can have a short break.

Do you have any questions or concerns before we start?

If you are happy to proceed, I will start the recording now and we can get started. The Interview will take approximately about 30 minutes.

Questions	**Probes**

Tell me about your exercise routine after your stroke.
 	
This includes any structured activity you do for the purpose of maintaining or improving your health.
	• Have you ever used any strategies since your stroke to help you complete this exercise regularly?
	  ○ E.g., exercise professional, training buddy, doing something you enjoy.
	• How have your exercise habits changed since your stroke?
	  ○ **If currently exercising** – what helped you with your return or starting of exercise since your stroke?
	  ▪ What strategies have you found useful in helping you maintain your exercise routine since your stroke?
	  ▪ Has a family member, carer or health professional helped with this?
	  • How/Why not?
	  ○ **If not currently exercising** – why do you not exercise since having your stroke?
	  ▪ What do you think may motivate you to start exercising since your stroke?
	  ○ Support from a family member, carer, or health professional?

On a scale of 1-10 (with 1 being not very important and 10 being very important), how important do you consider exercise since your stroke?	• Can you please tell me about why you picked that number?
	  ○ Why not a number lower?
	  ○ Why not a number higher?
	• What do you think may increase the importance you place on exercise since your stroke?

On a scale of 1-10 (with 1 being not very confident and 10 being very confident), how confident are you in completing exercise since your stroke?	• Can you please tell me about why you picked that number?
	  ○ Why not a number lower?
	  ○ Why not a number higher?
	• What do you think increase your confidence in completing exercise since your stroke?

One type of exercise is High Intensity Interval Training, also known as HIIT. What do you know about HIIT?	**If they know nothing about it or want more information –** HIIT is a form of exercise involving small bouts of higher effort exercise split up with small bouts of lower effort exercise. This may be completed using many different methods including on a bike, walking/running, boxing. • What are your thoughts on the title, High Intensity Interval Training?
On a scale of 1-10 (with 1 being not very willing and 10 being very willing), how willing would you be to complete a HIIT session if your therapist suggested it?	• Why not a number lower? • Why not a number higher? • What do you think may increase your willingness to complete a HIIT session since your stroke? ○ Would your willingness to complete HIIT change if you were told that HIIT has been shown to improve numerous outcomes for people after stroke

	including fitness, heart health and brain health. This may help improve day-to-day function, reduce risks of future stroke, and improve the brain's ability to learn and remember things. ▪ Why/Why not?
What are your thoughts on the title, High Intensity Interval Training?	

We have reached the end of the formal questions of this interview. Do you have anything else you would like to discuss?

Thank you very much for your time and thoughts on this topic. The information you have provided will be examined along with the answers provided in interviews with other stroke survivors. We will identify common themes and present this information at conferences and in stroke rehabilitation journals in a hope to improve rehabilitation practices. If you are interested, we can send you a copy of the results once completed. (if yes, email? post?).

Myself and my research team really appreciate your involvement in this study. I hope you have a lovely rest of your day/evening.

12.4 Appendix 4: Health professional semi-structured interview script

Good morning/afternoon and welcome. My name is Sarah Ashcroft, and I am a researcher with Australian Catholic University. Thank you again for agreeing to talk with me today.

This interview is part of a research project investigating the benefits of exercise after stroke. In particular, we have found that High Intensity Interval Training (HIIT), which is a form of aerobic exercise involving small amounts of high effort exercise broken up with small amounts of lighter effort exercise in between, has shown great benefits for the heart, muscles and brain after stroke. However, we are not sure what may be stopping people with stroke from participating in HIIT exercise, or what may help to motivate them to participate in HIIT. We hope to use this information to teach health professionals of ways to improve their therapy programs to ensure people with stroke are enjoying therapy and receiving the best benefits exercise can provide.

My research team and I are specifically interested in understanding your experience with exercise for people after stroke as well as your opinions on some of the strategies that you could use to improve the use of this type of exercise.

Today, I would like to cover a few different topics to get an idea of your thoughts on exercise after stroke and how you may recommend or prescribe it to people with stroke. Our chat will be focusing on:

- Your experience of recommending or prescribing exercise for people with stroke.
- Your thoughts on High Intensity Interval Training, or HIIT, after stroke.

This discussion is confidential – while we hope to present this information to researchers and health professionals, your name will not be used publicly so please do not hesitate to share your point of view. There are no right or wrong answers. We are recording the session, but the recordings will not be shared to anyone outside of the research team. If at any time you don't feel comfortable sharing your opinions or do not want to participate any further, you are free to not respond or withdraw at any time. Also, if any topics are uncomfortable for you, do let me know and we can have a short break.

Do you have any questions or concerns before we start?

If you are happy to proceed, I will start the recording now and we can get started. The Interview will take approximately about 30 minutes.

Questions	**Probes**
What is your role when you work with people after stroke?	
Tell me about your experience with exercise for people after stroke.	• What would you expect would be challenging for the people with stroke in doing exercise? • What kind(s) of exercise do you recommend or prescribe for people after stroke? • How do you think that you as a health professional might educate people after stroke on the importance of exercise?

On a scale of 1-10 (with 1 being not very important and 10 being very important), how important do you consider exercise for people with stroke?	• Can you please tell me about why you picked that number?
	  ○ Why would you consider exercise at that level of importance for a person with stroke?
	  ○ What do you think may increase the importance you place on people with stroke completing exercise?

In our interviews with people with stroke, I am providing the following definition of High Intensity Interval Training, also known as HIIT:
HIIT is a form of exercise involving small bouts of higher effort exercise split up with small bouts of lower effort exercise. This may be completed using many different methods including on a bike, walking/running, boxing.
	• Can you tell me about your experience with HIIT for people with stroke?
	• What would you consider the benefits of a HIIT program for people with stroke?
	  ○ What about improvements in fitness, heart health and brain health?
	If they have recommended/prescribed HIIT before:
	• How did you select the people with stroke to recommend/prescribe HIIT to?
	  ○ E.g., evidence– based evidence/criteria/goals/patient request?

	• What guided your recommendation/prescription of HIIT?
	  ○ How did you choose the effort levels used?
	  ○ How did you monitor effort level?
	  ○ Did you test cardiorespiratory fitness prior to commencement?
	• Have you been trained to recommend/prescribe HIIT to a person with stroke?
	  ○ Where did you receive this training?
	  ○ Do you have any suggestions for how the recommendation/prescription of HIIT (and the necessary training to do so) can be promoted to other health professionals working with people with stroke?
	
	If they have not used HIIT:
	• Why have you not recommended or prescribed HIIT to a person with stroke?

On a scale of 1-10 (with 1 being not very willing and 10 being very willing), how willing would you be to recommend/prescribe HIIT to a person with stroke?	• Why not a number lower?
	• Why not a number higher?
	• What do you think may increase your willingness to recommend/prescribe HIIT to a person with stroke?
	• What would you consider the benefits of a HIIT program for people with stroke?
	  ○ What about improvements in fitness, heart health and brain health?
	  ▪ Would this change your opinion?

	• How might a health professional encourage people with stroke to become involved in HIIT?
	  ○ What are your thoughts on the title, HIIT?
	  ○ What are your thoughts on when HIIT should be started after stroke? For example, how long after stroke do you think this is safe to start?

What are your thoughts on which health professional should supervise a HIIT session of a person after stroke?	•

We have reached the end of the formal questions of this interview. Do you have anything else you would like to discuss?

Thank you very much for your time and thoughts on this topic. The information you have provided will be examined along with the answers provided in interviews with other health professionals who work with people with stroke. We will identify common themes and present this information at conferences and in stroke rehabilitation journals in a hope to improve rehabilitation practices. If you are interested, we can send you a copy of the results once completed. (If yes, email? post?).

Myself and my research team really appreciate your involvement in this study. I hope you have a lovely rest of your day/evening.

12.5 Appendix 5: Submaximal graded exercise test protocol (modified from Yates et al., 2004)

Submaximal Cycle Test

Age: _____ years
Sex: M / F

Estimated HR_{max}: _____ bpm
90% HR_{max}: _____ bpm

Pre-test venous blood taken? Y / N

Pre-Test Measures:
Heart rate: _____ bpm
Blood pressure: _____/_____ mmHg
SaO_2: _____ %
Pre-test blood lactate: _____ mmol/L

Time (min)	Cadence (RPM)	Resistance kP	Power (W)	HR (bpm)	RPE	SaO_2 (%)
1	70	0.5	35			
2						
3						
4	70	1	70			
5						
6						
7		1.5	105			
8						
9						
10		2	140			
11						
12						
13		2.5	175			
14						
15						
16	80 / 85 / 90	2.5 / 3				
17						
18						

Reason for termination: **Time of termination:** ____min ____sec

☐ Maximal effort (e.g. 90% HR_{max} or 18/20 RPE) ☐ Other: _____
☐ Symptoms of angina, dyspnoea and/or fatigue ☐ SaO_2 <85%
☐ Voluntary exhaustion or inability to maintain cycling cadence set by clinician

Post-test venous blood taken? Y / N

Post-Test Measures:
Heart rate: _____ bpm
Blood pressure: _____/_____ mmHg
SaO_2: _____ %
Post-test blood lactate: _____ mmol/L

12.6 Appendix 6: Ethics approval mixed methods study

Subject: [2022-2702H] - Ethics application approved!
Date: Monday, 20 February 2023 at 9:33:06 am Australian Eastern Daylight Time
From: Tanya Quesnel on behalf of Res Ethics
To: Angelica Thompson-Butel, Liam Johnson, Suzanne Kuys
CC: Res Ethics, Sarah Ashcroft

Dear Applicant,

Chief Investigator: Dr Angelica Thompson Butel, Professor Suzanne Kuys, and Dr Liam Johnson Student Researcher: Miss Sarah Ashcroft
Ethics Register Number: 2022-2702H
Project Title: PeRsonalised Exercise for Priming Post-stroke (PREPP): Survivors and Health Professionals Views
Date Approved: 20/02/2023
End Date: 29/02/2024

This is to certify that the above human ethics application has been reviewed by the Australian Catholic University Human Research Ethics Committee (ACU HREC). The application has been approved for the period given above.

Continued approval of this research project is contingent upon the submission of an annual progress report which is due on/before each anniversary of the project approval. A final report is due upon completion of the project. A report proforma can be downloaded from the ACU Research Ethics website.

Researchers are responsible for ensuring that all conditions of approval are adhered to and that any modifications to the protocol, including changes to personnel, are approved prior to implementation. In addition, the ACU HREC must be notified of any reportable matters including, but not limited to, incidents, complaints and unexpected issues.

Researchers are also responsible for ensuring that they adhere to the requirements of the National Statement on Ethical Conduct in Human Research, the Australian Code for the Responsible Conduct of Research and the University's Research Code of Conduct.

Any queries relating to this application should be directed to the Ethics Secretariat (res.ethics@acu.edu.au). Please quote your ethics approval number in all communications with us. We wish you every success with your research.

Kind regards,
Tanya Quesnel
on behalf of ACU HREC Chair, Assoc Prof. Michael Baker

Research Ethics Officer | Research Services | Office of the Deputy Vice-Chancellor

(Research) Australian Catholic University

T: +61 2 9739 2646 E: res.ethics@acu.edu.au

12.7 Appendix 7: Royal Prince Alfred ethics approval intervention studies

ADDRESS FOR ALL CORRESPONDENCE

RESEARCH ETHICS AND GOVERNANCE OFFICE
ROYAL PRINCE ALFRED HOSPITAL CAMPERDOWN NSW 2050
TELEPHONE: (02) 9515 6766
EMAIL: SLHD-RPAEthics@health.nsw.gov.au

REFERENCE: X21-0095 & 2021/ETH00633 **10.11/MAY21**

11 May 2021

This letter constitutes ethical approval only. You must NOT commence this research project at ANY site until you have submitted a Site Specific Assessment Form to the Research Governance Officer and received separate authorisation from the Chief Executive or delegate of that site.

Dear Dr Thompson-Butel,

Re: Protocol No X21-0095 & 2021/ETH00633 - "Personalised Exercise for Priming and Prevention Post-stroke (PEPPP)"

The Executive of the Ethics Review Committee, at its meeting of 11 May 2021 considered your correspondence of 8 May 2021. In accordance with the decision made by the Ethics Review Committee at its meeting of 14 April 2021, ethical approval is granted.

- The research project meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

This approval includes the following:

- HREA (Version 3, 30 April 2021)
- Protocol (Version 2, 22 April 2021) * see additional condition below
- Flyer (Version 1, 12 April 2021)
- Participant Information Sheet (Version 3, 5 May 2021)
- Participant Consent Form (Version 3, 5 May 2021)
- Withdrawal of Participation (Version 3, 5 May 2021)
- Serious Adverse Event Log (Version 1, 1 April 2021)
- Research Data Management Plan (Version 1, 2 April 2021)
- Master Code Sheet (Version 1, 1 April 2021) Data Collection Forms:
- Arm Reach Action Test (ARAT) (Version 1, 1 April 2021)
- Box and Block Test (Version 1, 1 April 2021
- Grooved Pegboard Test (Version 1, 1 April 2021)

- Motor Activity Log (Quality of Movement Scale) (Version 1, 1 April 2021)
- Modified Rankin Scale (mRS) (Version 1, 1 April 2021)
- NIH Stroke Scale (NIHSS) (Version 1, 1 April 2021)
- Upper Limb Fugl-Meyer Assessment (Version 1, 1 April 2021)
- 6 Minutes Walk Test (Version 1, 1 April 2021)
- 10 Metre Walk Test (Version 1, 1 April 2021)
- Case Report (Version 1)
- Goal Setting and Problem Solving (Version 1, 1 April 2021) Submaximal Cycle Test (Version 1, 1 April 2021)

*(If applicable) In accordance with the National Statement, chapter 4.7; you must seek ethical approval from the HREC of the Aboriginal Health and Medical Research Council (AHMRC) if you intend to use ATSI status in any presentation or publication.

The Committee noted that authorisation will be sought to conduct the study at the following site:

- Royal Prince Alfred Hospital
- St Joseph's Hospital, Auburn
- Australian Catholic University, Strathfield
- Metro Rehab Hospital, Petersham
- This approval is valid for **five** years, and the Committee requires that you furnish it with annual reports on the study's progress beginning in **May 2022.** If recruitment is ongoing at the conclusion of the five year approval period, a full re-submission will be required. Ethics approval will continue during the re-approval process.
- This human research ethics committee (HREC) has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review and is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.
- You must immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- You must notify the HREC of proposed changes to the research protocol or conduct of the research in the specified format.
- You must notify the HREC and other participating sites, giving reasons, if the project is discontinued at a site before the expected date of completion.

- If you or any of your co-investigators are University of Sydney employees or have a conjoint appointment, you are responsible for informing the University's Risk Management Office of this approval, so that you can be appropriately indemnified.

- Where appropriate, the Committee recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purposes of conducting this study.

Should you have any queries about the Committee's consideration of your project, please contact me. The Committee's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Sydney Local Health District website.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The Ethics Review Committee wishes you every success in your research.

Yours sincerely,

Merela Ghazal
Acting Executive Officer Ethics Review Committee (RPAH Zone)

HERC\COR\21-05

12.8 Appendix 8: Royal Rehab Private Petersham (formerly MetroRehab Hospital) ethics approval intervention studies

25 June 2021

Dr Angelica Thompson-Butel
Australian Catholic University
School of Allied Health
167-169 Albert Road
Strathfield NSW 2135

Sent via email: Angelica.ThompsonButel@acu.edu.au
CC: Sarah Ashcroft; sarahkashcroft@gmail.com

Dear Dr Thompson-Butel

AUTHORISATION OF SSA APPLICATION

Protocol No X21-0095 & 2021/ETH00633 - "Personalised Exercise for Priming and Prevention Post-stroke (PEPPP)"

Thank you for submitting the above Site-Specific Assessment (SSA) for application for research to be conducted using clients of MetroRehab Hospital, Petersham who have been discharged and returned to the community.

The application has been reviewed and authorised by the Chief Executive Officer's delegate and will now be monitored by Royal Rehab's Research Governance Office (RGO).

The authorisation relates to the following documentation:

Document	Version	Date
Human Research Ethics Application (HREA)	Version 3	30 April 2021
HREA Approval by SLHD Human Research Ethics Committee (HREC)	Version 1	11 May 2021
Flyer	Version 1	12 April 2021
Participant Information Sheet	Version 3	5 May 2021
Participant Consent Form	Version 3	5 May 2021
Withdrawal of Participation	Version 3	5 May 2021
Serious Adverse Event Log	Version 1	1 April 2021

Research Data Management Plan	Version 1	2 April 2021
Master Code Sheet	Version 1	1 April 2021

Please note the following conditions of authorisation:

- Consistent with Sydney Local Health District's Human Research Ethics Committee decision of 11 May 2021, your authorisation to conduct research at MetroRehab, directly relating to this project, will remain active for five years.

  - Any extension to this timeframe will require submission of a revised HREA and subsequent approval from the SLHD HREC, and submission of approval of extension to MetroRehab.

- As the Principal Investigator, you must ensure that any proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, are submitted through REGIS to the lead HREC for review, and copied to the RGO;

  - any proposed amendments to the research protocol or conduct of the research which may affect the ongoing acceptability of the project for MetroRehab, are submitted to the RGO; and

  - all appropriate documentation is submitted to the RGO, and authorisation is received, before any external researcher conducts research at MetroRehab.

- MetroRehab requests a copy of your annual progress report, at the same time it is provided to the HREC. The first report is due by May 2022.

- You must also provide a full report to the RGO at the completion of your study.

MetroRehab wishes you all the best with your research.

Please contact either myself at nick.edwards@metrorehab.com.au or phone +61 2 8585 4900 if you would like to discuss any aspects of this process further.

Yours Sincerely

Nicholas Edwards
General Manager

12.9 Appendix 9: ACU ethics approval intervention studies

Subject: [2022-2698RC] - Ethics application approved!
Date: Thursday, 19 May 2022 at 5:28:41 pm Australian Eastern Standard Time **From:** Leanne S5rling on behalf of Res Ethics
To: Angelica Thompson-Butel
CC: Res Ethics, Sarah Ashcroft, Kerrie Basclain, Suzanne Kuys, Liam Johnson

Dear Applicant,

Chief Inves5gator: Dr Angelica Thompson Butel
Professor Suzanne Kuys, Dr Liam Johnson, Dr Kerrie Basclain, Dr Chris5ne Shiner, Catherine Woolnough, Student Researcher: Sarah Ashcroft
Ethics Register Number: 2022-2698RC
Project Title: PeRsonalised Exercise for Priming Post-stroke (PREPP): A randomised trial
Date Approved: 19/05/2022
End Date: 29/02/2024

*** Approval beyond this date is subject to the submission of annual progress reports to the governing HREC. A copy of annual reports and evidence of acceptance by the governing HREC should be provided to res.ethics@acu.edu.au.**

The Australian Catholic University Human Research Ethics Committee has considered your registration of an externally approved human ethics application and notes that this application has been reviewed by Royal Prince Alfred Hospital HREC, External HREC Reference: X21-0432

The ACU HREC accepts the approval with no additional requirements, save that the ACU HREC is informed of any modifications to the research proposal and that copies of all progress reports, final reports and any other documents be forwarded to it. Any reportable matters, complaints or incidents must also be notified to the ACU HREC (National Statement 5.3.3). Please note that regardless of the jurisdiction the research project will take place in, you must comply with Australian standards as per the NHMRC National Statement.

Any queries relating to this application should be directed to the Ethics Secretariat (res.ethics@acu.edu.au). Please quote your ethics approval number in all communications with us.

We wish you every success with your research.

Kind regards,

Leanne Stirling
on behalf of ACU HREC Chair, Assoc Prof. Michael Baker

Research Ethics Officer | Research Services | Office of the Deputy Vice-Chancellor (Research) Australian Catholic University
T: +61 2 9739 2646 E: res.ethics@acu.edu.au

12.10 Appendix 10: Full search strategy of systematic review and meta-analysis

Database	Actual search strategy applied	Results
APA Thesaurus of Psychological Index Terms	S1. Stroke* OR “stroke survivor” OR (cerebro*vascular) N1 (accident OR attack OR event) OR CVA OR (h#emorrhag* OR isch#emi*) N1 (cerebral OR brain) S2. (Aerobic OR “cardio*vascular” OR endurance OR cardio* OR resistance OR strength OR weight* OR balance OR propriocepti* OR co*ordination OR “dual*task*” OR stretching OR flexibility) N1 (exercise* OR therapy OR training) OR (exercise OR physical OR movement OR motor) N1 (prescription OR therapy OR rehab*) OR “physical activity” S3. “Brain*derived neurotrophic factor” OR BDNF OR “neurotrophic factor” S4. S1 AND S2 AND S3	183
CINAHL	1. Stroke* OR “stroke survivor” OR (cerebro*vascular) N1 (accident OR attack OR event) OR CVA OR (h#emorrhag* OR isch#emi*) N1 (cerebral OR brain) 2. (Aerobic OR “cardio*vascular” OR endurance OR cardio* OR resistance OR strength OR weight* OR balance OR propriocepti* OR co*ordination OR “dual*task*” OR stretching OR flexibility) N1 (exercise* OR therapy OR training) OR (exercise OR physical OR movement OR motor) N1 (prescription OR therapy OR rehab*) OR “physical activity” 3. “Brain*derived neurotrophic factor” OR BDNF OR “neurotrophic factor” 4. (MH "Stroke") OR (MH "Cerebral Infarction") OR (MH "Hemorrhagic Stroke") OR (MH "Ischemic Stroke") OR (MH "Stroke Patients") OR (MH "Embolic Stroke") OR "cerebrovascular attack"	149

Database	Actual search strategy applied	Results
	5. (MH "Endurance Training") OR (MH "High-Intensity Interval Training") OR (MH "Exercise") OR (MH "Lower Extremity Exercises") OR (MH "Muscle Strengthening") OR (MH "Pilates") OR (MH "Plyometrics") OR (MH "Stretching") OR (MH "Upper Extremity Exercises") OR (MH "Core Exercises") OR (MH "Group Exercise") OR (MH "Callisthenics") OR (MH "Back Exercises") OR (MH "Aerobic Exercises") OR (MH "Anaerobic Exercises") OR (MH "Abdominal Exercises") OR (MH "Physical Activity") OR (MH "Physical Fitness") OR (MH "Physical Performance") OR (MH "Sports") OR (MH "Physical Therapy") 6. (MH "Brain-Derived Neurotrophic Factor") 7. S1 AND S2 AND S3 8. S4 AND S5 AND S6 9. S7 OR S8	
Embase Classic + Embase	1. Stroke or "stroke survivor" or "cerebro*vascular accident" or "cerebro*vascular attack" or "cerebro*vascular event" or CVA or "cerebral h#emorrhag*" or "brain h#emorrhag*" or "cerebral isch#emi*" or "brain isch#emi*" 2. "Aerobic exercise*" OR "aerobic therapy" OR "aerobic training" OR "cardio*vascular exercise*" OR "cardio*vascular therapy" OR "cardio*vascular training" OR "endurance exercise*" OR "endurance therapy" OR "endurance training" OR "cardio* exercise*" OR "cardio* therapy" OR "cardio* training" OR "resistance exercise*" OR "resistance therapy" OR "resistance training" OR "strength exercise*" OR "strength therapy" OR "strength training" OR "weight*training" OR "weight*exercise*" OR "weight* therapy" OR "balance exercise*" OR "balance therapy" OR "balance training" OR "propriocepti* exercise*" OR "propriocepti* therapy" OR "propriocepti* training" OR "co*ordination exercise*" OR "co*ordination therapy" OR "co*ordination training"	175

Database	Actual search strategy applied	Results
	OR "dual*task exercise*" OR "dual*task therapy" OR "dual*task training" OR "stretch* exercise*" OR "stretch* therapy" OR "stretch* training" OR "flexibility exercise*" OR "flexibility therapy" OR "flexibility training" OR "exercise prescription" OR "exercise therapy" OR "exercise rehab*" OR "physical prescription" OR "physical therapy" OR "physical rehab*" OR "movement prescription" OR "movement therapy" OR "movement rehab*" OR "motor prescription" OR "motor therapy" OR "motor rehab*" OR "physical activity" 3. "Brain*derived neurotrophic factor" or BDNF or "neurotrophic factor" 4. 1 AND 2 AND 3	
Medline	S1. Stroke* OR “stroke survivor” OR (cerebro*vascular) N1 (accident OR attack OR event) OR CVA OR (h#emorrhag* OR isch#emi*) N1 (cerebral OR brain) S2. (Aerobic OR “cardio*vascular” OR endurance OR cardio* OR resistance OR strength OR weight* OR balance OR propriocepti* OR co*ordination OR “dual*task*” OR stretching OR flexibility) N1 (exercise* OR therapy OR training) OR (exercise OR physical OR movement OR motor) N1 (prescription OR therapy OR rehab*) OR “physical activity” S3. “Brain*derived neurotrophic factor” OR BDNF OR “neurotrophic factor” S4. (MH “Stroke”) OR (MH “Ischemic Stroke”) OR (MH “Hemorrhagic Stroke”) OR (MH “Stroke Rehabilitation”) OR (MH “Cerebral Intraventricular Hemorrhage”) OR (MH “Cerebral Hemorrhage”) S5. (MH “Exercise”) OR (MH “Plyometric Exercise”) OR (MH “Exercise Therapy”) OR (MH “Cool-down Exercise”) OR (MH “Warm-up Exercise”) OR (MH “Endurance Training”) OR (MH “Muscles Stretching Exercises”) OR (MH “Resistance Training”) OR (MH “High-Intensity Interval Training”) OR (MH “Weight Lifting”) OR (MH “Breathing	1,111

Database	Actual search strategy applied	Results
	Exercises") OR (MH "Exercise Movement Techniques") OR (MH "Circuit-Based Exercise") OR (MH "Physical Therapy Modalities") OR (MH "Rehabilitation") OR (MH "Physical and Rehabilitation Medicine") OR (MH "Neurological Rehabilitation") S6. (MH "Brain-Derived Neurotrophic Factor") S7. S1 OR S4 S8. S2 OR S5 S9. S3 OR S6 S10. S7 AND S8 AND S9	
PubMed	#1. Stroke OR "stroke survivor" OR "cerebrovascular accident" OR "cerebrovascular attack" OR "cerebrovascular event" OR "cerebro-vascular accident" OR "cerebro-vascular attack" OR "cerebro-vascular event" OR CVA OR "cerebral hemorrhag*" OR "brain hemorrhag*" OR "cerebral ischemi*" OR "brain ischemi*" OR "cerebral haemorrhag*" OR "brain haemorrhag*" OR "cerebral ischaemi*" OR "brain ischaemi*" #2. "Aerobic exercise*" OR "aerobic therapy" OR "aerobic training" OR "cardiovascular exercise*" OR "cardiovascular therapy" OR "cardiovascular training" OR "cardio-vascular exercise*" OR "cardio-vascular therapy" OR "cardio-vascular training" OR "endurance exercise*" OR "endurance therapy" OR "endurance training" OR "cardio* exercise*" OR "cardio* therapy" OR "cardio* training" OR "resistance exercise*" OR "resistance therapy" OR "resistance training" OR "strength exercise*" OR "strength therapy" OR "strength training" OR "weight* exercise*" OR "weight* therapy" OR "weight* training" OR "balance exercise*" OR "balance therapy" OR "balance training" OR "proprioception exercise*" OR "proprioception therapy" OR	317

Database	Actual search strategy applied	Results
	“proprioception training” OR “proprioceptive exercise*” OR “proprioceptive therapy” OR “proprioceptive training” OR “coordination exercise*” OR “coordination therapy” OR “coordination training” OR “co-ordination exercise*” OR “co-ordination therapy” OR “co-ordination training” OR “dual task* exercise*” OR “dual task* therapy” OR “dual task* training” OR “dual-task* exercise*” OR “dual-task* therapy” OR “dual-task* training” OR “stretching exercise*” OR “stretching therapy” OR “stretching training” OR “flexibility exercise*” OR “flexibility therapy” OR “flexibility training” OR “exercise prescription” OR “exercise therapy” OR “exercise rehab*” OR “physical prescription” OR “physical therapy” OR “physical rehab*” OR “movement prescription” OR “movement therapy” OR “movement rehab*” OR “motor prescription” OR “motor therapy” OR “motor rehab*” OR “physical activity” #3. “Brain-derived neurotrophic factor” OR “brain derived neurotrophic factor” OR BDNF OR “neurotrophic factor” #4. "Stroke"[Mesh] OR "Hemorrhagic Stroke"[Mesh] OR "Ischemic Stroke"[Mesh] OR "Stroke Rehabilitation"[Mesh] #5. "Exercise"[Mesh] OR "Circuit-Based Exercise"[Mesh] OR "Cool-Down Exercise"[Mesh] OR "Warm-Up Exercise"[Mesh] OR "Plyometric Exercise"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Exercise Therapy"[Mesh] OR "Resistance Training"[Mesh] OR "Muscle Stretching Exercises"[Mesh] OR "High-Intensity Interval Training"[Mesh] OR "Breathing Exercises"[Mesh] #6. "Endurance Training"[Mesh] #7. "Brain-Derived Neurotrophic Factor"[Mesh] OR "BDNF protein, human" [Supplementary Concept]	

Database	Actual search strategy applied	Results
	#8. #5 OR #6 #9. #1 OR #4 #10. #2 OR #8 #11. #3 OR #7 #12. #9 AND #10 AND #11	
SportDiscus	S1. Stroke* OR “stroke survivor” OR (cerebro*vascular) N1 (accident OR attack OR event) OR CVA OR (h#emorrhag* OR isch#emi*) N1 (cerebral OR brain) S2. (Aerobic OR “cardio*vascular” OR endurance OR cardio* OR resistance OR strength OR weight* OR balance OR propriocepti* OR co*ordination OR “dual*task*” OR stretching OR flexibility) N1 (exercise* OR therapy OR training) OR (exercise OR physical OR movement OR motor) N1 (prescription OR therapy OR rehab*) OR “physical activity” S3. “Brain*derived neurotrophic factor” OR BDNF OR “neurotrophic factor” S4. S1 AND S2 AND S3 S1. Stroke* OR “stroke survivor” OR (cerebro*vascular) N1 (accident OR attack OR event) OR CVA OR (h#emorrhag* OR isch#emi*) N1 (cerebral OR brain) S2. (Aerobic OR “cardio*vascular” OR endurance OR cardio* OR resistance OR strength OR weight* OR balance OR propriocepti* OR co*ordination OR “dual*task*” OR stretching OR flexibility) N1 (exercise* OR therapy OR training) OR (exercise OR physical OR movement OR motor) N1 (prescription OR therapy OR rehab*) OR “physical activity” S3. “Brain*derived neurotrophic factor” OR BDNF OR “neurotrophic factor”	10

Database	Actual search strategy applied	Results
	S4. S1 AND S2 AND S3	
Web of Science Core Collection	#1. ALL FIELDS: (Stroke* OR "stroke survivor" OR (cerebro*vascular) N1 (accident OR attack OR event) OR CVA OR (h?emorrhag* OR isch?emi*) N1 (cerebral OR brain)) #2. ALL FIELDS: ((Aerobic OR "cardio*vascular" OR endurance OR cardio* OR resistance OR strength OR weight* OR balance OR propriocepti* OR co*ordination OR "dual*task*" OR stretching OR flexibility) N1 (exercise* OR therapy OR training) OR (exercise OR physical OR movement OR motor) N1 (prescription OR therapy OR rehab*) OR "physical activity") #3. ALL FIELDS: ("Brain*derived neurotrophic factor" OR BDNF OR "neurotrophic factor") #4. #1 AND #2 AND #3 #5. TOPIC: (Stroke* OR "stroke survivor" OR (cerebro*vascular near/1 (accident OR attack OR event)) OR CVA OR (h?emorrhag* OR isch?emi* near/1 (cerebral OR brain))) #6. TOPIC: (((Aerobic OR "cardio*vascular" OR endurance OR cardio* OR resistance OR strength OR weight* OR balance OR propriocepti* OR co*ordination OR "dual*task*" OR stretching OR flexibility) near/1 (exercise* OR therapy OR training) OR ((exercise OR physical OR movement OR motor) near/1 (prescription OR therapy OR rehab*)) OR "physical activity") #7. TOPIC: ("Brain*derived neurotrophic factor" OR BDNF OR “neurotrophic factor") #8. #5 AND #6 AND #7 #9. #4 OR #8	250

12.11 Appendix 11: Thematic analysis for mixed methods study

General exercise thematic analysis:

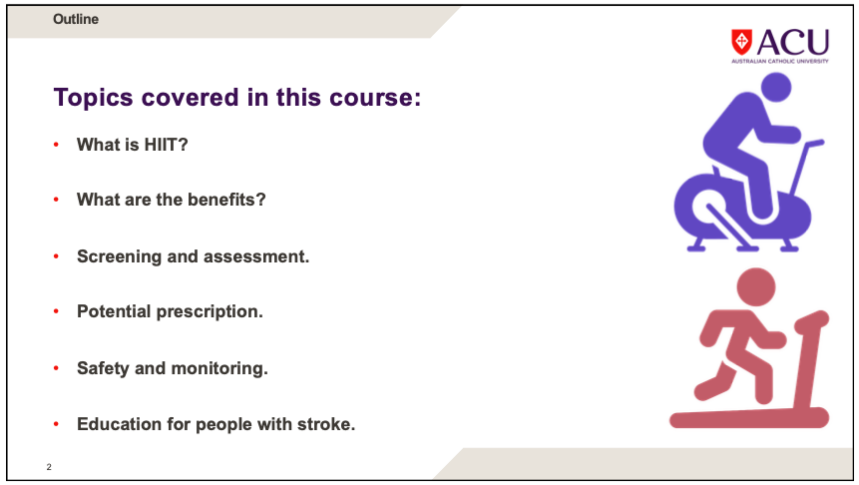
Theme	Sub-theme	People with stroke (PwS)	Health professionals (HP)
Exercise is beneficial after stroke	**Clear role of exercise in stroke recovery**	**PwS3:** "It's trying to get back to normality". **PsW8:** "[hospital staff] tried to tell me that the more I do, the better it is…move it or lose it". "I'm wanting to get better than I am now".	**HP1:** "I think it's important, like if people want to regain function or minimise their risk of another stroke then it's the best way to do it, obviously alongside their medical management".
	Physical benefits of exercise after stroke	**PwS3:** "Exercise to keep you going and your body moving I think is very important". **PwS5:** "So for me, you know exercise that way [for my balance] I think is very important". **PwS7:** "I was weak, and I still am, so it's important to do strength-based exercise".	**HP1:** "The cardiovascular benefits [of aerobic exercise] and I think for a lot of strokes, there is obviously that secondary deconditioning alongside their stroke impairment". **HP3:** "It's important for general health and fitness". **HP5:** "Going to help them prevent a future stroke". "People with strokes may have other comorbidities, so that's going to help assist that as well, improving their respiratory system…so really trying to prevent…future complications as well".
	Mental benefits of exercise after stroke	**PwS4:** "I find it harder now, but I think it's really good for your mental health, particularly for me…physically I haven't had a lot of deficits, but I've mentally struggled, and I think exercise is really important to get you out and about, move your body…your body feels good, your mind feels good". **PwS6:** "It keeps me sane. It's an antidepressant thing, which is an issue with stroke". **PwS7:** "It's also the social aspect of doing exercise". **PwS8:** "I'm hoping the neuroplasticity will kick in". **PwS10:** "It's meant to develop neuroplasticity".	**HP1:** "Improves blood perfusion to the brain and that's gonna have benefits to potentially cognition". **HP3:** "Quality of life". **HP4:** "I think having a group of like-minded people together and working in a…group setting does help to improve self-efficacy because you've got that socialisation and seeing someone else do it". **HP8:** "I think the group stuff is really helpful because…they can see that there are people like them that are doing exercise and have benefits. And they can also socialise…it's not only going to benefit mental health, but it's something to come for".
Stroke impairments impact exercise after stroke	**Stroke impairments reduce confidence with exercise participation after stroke**	**PwS3:** "Confidence got a big hit when I had a stroke and it's always about falling. I've already done a hip [from a fall] and I don't want to go back there. Call it PTSD". **PwS4:** "I've lost a bit of confidence. Not because I think I'm gonna have another stroke…it's just the confidence in, 'Is this going to make me too tired?...Am I going to feel sick or bad? Is tomorrow going to be worse if I've got lots to do today?'".	

Stroke impairments impact exercise after stroke	**Stroke impairments impact prescription of exercise after stroke**		**HP1:** "I guess their mobility. I think fatigue also factors in. Maybe like the severity of the loss of function they've experienced". **HP3:** "Depending on the severity of their stroke and their function or disability, what they can do…". **HP6:** "Depends on what stage of the stroke recovery they're at". "…I think for some people there's that fear of exerting themselves too much and what implications that will have on what they can do for the rest of the day or week".
Experience increases confidence with exercise after stroke	**Exercise history impacts involvement in exercise after stroke**	**PwS1:** "I think you gain confidence by doing…I'm confident because I've continued to exercise, and if I drop off, my confidence would drop off as well". **PwS2:** "I think I've got a history of being adverse to exercise".	**HP7:** "Previous history, so before injury what the physical activity levels were like at that point".
	Monitoring exercise may impact facilitation of exercise after stroke	**PwS1:** "…You look at your little thing on your iPhone or however you are keeping it and try and build your program". **PwS4:** "Going with people, with friends or with my partner, I sort of force myself to get up". **PwS5:** "I think just seeing where I was before in hospital and seeing what I've come to".	**HP1:** "Give people the Borg scale and just be like, 'We're trying to get you working at this level', or, 'So you can speak, but like you're a bit breathless but able to still say words'". **HP3:** "We have another second person, usually [an] allied health assistant or another physio". **HP4:** "Tracking outcome measures and showing them that they're changing over time helps".
Working with health professionals increases facilitation of exercise after stroke	**Health professionals must understand the participant**	**PwS1:** "As long as the health professional understood the challenges with each [person]". **PwS2:** "One on one chat". **PwS7:** "Training of fitness instructors to really understand fatigue". "Instructors that are very focused on going at your own pace, so it's pretty ideal for you know, my condition".	**HP2:** "I think it's really important to know how each of your clients' functions and what their routine looks like…and them more as a person. I term it 'professional friendship'…I think it's a bit of give and take". **HP3:** "Ask the person's preference because we always take into account their preference, what they like to do".
	Participant education is necessary		**HP4:** "Many don't understand it unless if they've got some medical background or health training…it requires a bit of education for them to understand the importance of it". **HP5:** "It needs to be a whole multidisciplinary education about how important exercise it". **HP6:** "It should be a team approach that secondary prevention needs to be done".

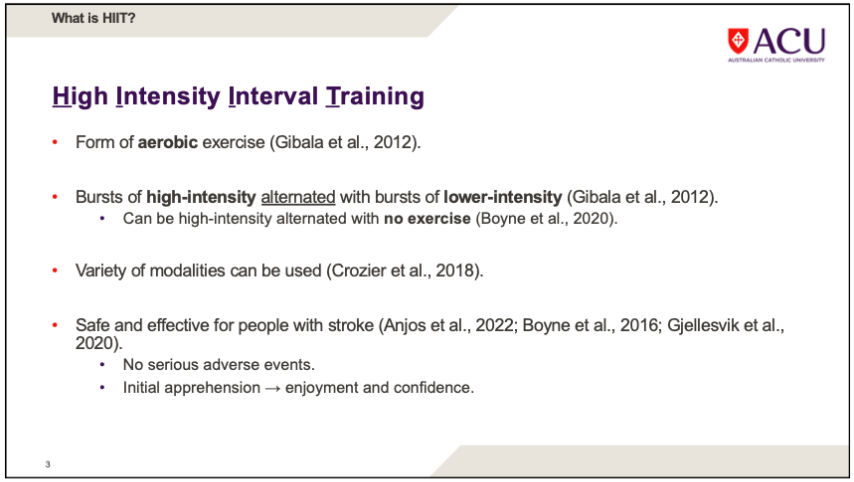
Working with health professionals increases facilitation of exercise after stroke	**Health professionals with expertise in exercise are recommended after stroke**	**PwS1:** "I'm just thinking of the health professionals, and physios, the osteos". **PwS3:** "[exercise] would only be through the exercise physiologist or through the physio or through my carer". **PwS7:** "Assessing good advice is the thing I'll probably come back to".	
	Health professionals are concerned about participant safety		**HP1:** "It's always safety and setup, it's sometimes a bit of a barrier". **HP3:** "Safety is one of those factors to consider". **HP8:** "I really think, prescribing exercise for fatigue is so unclear. Especially when it comes to cardio exercise".

12.12 Appendix 12: Example lecture for education to the multidisciplinary team

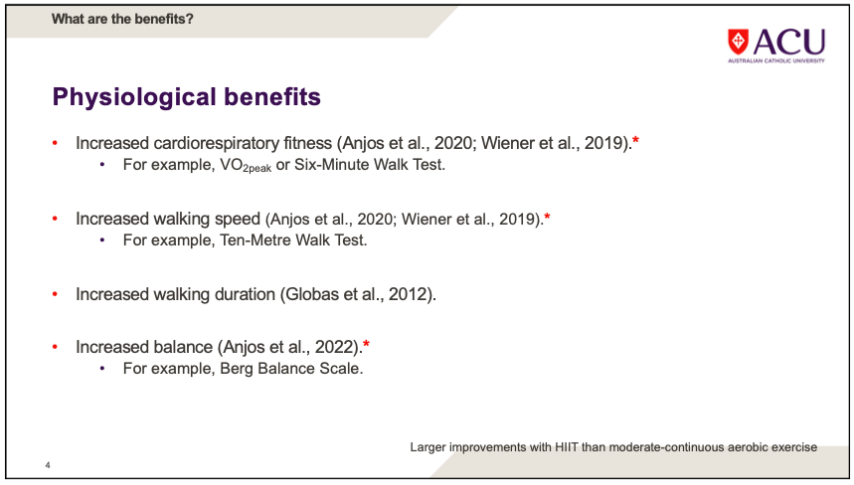
1



2



3



4

Neurological benefits

- Increase Brain-Derived Neurotrophic Factor – a marker of neuroplasticity (Boyne et al., 2020; Hsu et al., 2021).
  - Higher Brain-Derived Neurotrophic Factor associated with better prognosis (Wlodarczyk et al., 2021).
  - Increases seen with one single session (Boyne et al., 2020) and a program (Hsu et al., 2021).
- May facilitate greater motor skill retention when completed before training (Nepveu et al., 2017).

Other benefits

- Increased quality-adjusted life years (Hornby et al., 2022).
- Improvements in quality of life (Soh et al., 2020).
  - For example, European Quality of Life – 5 Dimension.
- Improved skill retention (Nepveu et al., 2017).
  - For example, a time-on-target motor task.
- Enjoyment (Boyne et al., 2016).
- Reduced stroke risk if 'vigorous' exercise is completed ≥2 times per week (Rist et al., 2011).

Screening

- Medical clearance is required before HIIT can be undertaken (Macko, 2016).
- Exercise and Sport Science Australia (ESSA) Adult Pre-Exercise Screening System can be completed prior to commencement (APPS, version 2, ESSA, 2019).
  - Guidance from an allied health or medical practitioner recommended.

Baseline assessment

- Symptom-limited or submaximal exercise test should be completed before HIIT (MacKay-Lyons et al., 2020).
  - ECG monitoring is recommended if available.
  - Heart rate, blood pressure and oxygen saturation monitored (Hsu et al., 2021).
- Exercise testing used to quantify exercise intensity.
  - For example:
    - Percentage of $HR_{max.}$
    - Percentage of $VO_{2peak.}$

Medical clearance

- Medical clearance required before commencement (Macko et al., 2016).
  - For example, GP, cardiologist.
  - Ensure the demands of HIIT are clearly outlined → Intervals, 'relative/personalised' high intensity, supervised, monitoring.
- Guidance from a health an appropriate allied health or medical professional required prior to commencement (APSS, version 2, ESSA, 2019).

Proposed FITT principle

Frequency	2-3 sessions per week (Anjos et al., 2020; Crozier et al., 2018)
Intensity	**ON:** 80-90% VO_{2peak} (Hsu et al., 2021). **OFF:** 40% VO_{2peak} (Hsu et al., 2021).
Time	25–30-minute session (Crozier et al., 2018). **ON:** 30-seconds to 3-minutes (Crozier et al., 2018). **OFF:** 30-seconds to 4-minutes (Crozier et al., 2018).
Type	Treadmill. Cycle ergometer. Stepper. (Crozier et al., 2018)
Duration of program	≥4 weeks for any benefit (Crozier et al., 2018). 4-15 weeks for increase in function (Anjos et al., 2020). 12-18 weeks for BDNF increase (Hsu et al., 2021)

Monitoring

- Heart rate.
- Blood pressure.
- Rate of Perceived Exertion (Borg, 1970).
- Oxygen saturation.

(Crozier et al., 2018; Hsu et al., 2021)

- Talk test may be used as an adjunct.

Home exercise

- Safe and feasible (Krawcyk et al., 2019).

Complete HIIT with client before recommending home exercise:

- Ensure client can self-monitor → RPE and/or heart rate.
- Educate client on fatigue/DOMS.
- Educate client on safe methods at home.
  - For example, location, medication, carrying a phone/with a friend.

Education about what HIIT is

- **Don't** use the words "high intensity".
- Emphasise the level of work is relative to them – *"what you think is harder on that day".*
  - Will fluctuate in accordance with fatigue levels.
- *"A program of aerobic exercise where you will be working a little harder for a short time and then working at a lighter pace to recover may be useful after your stroke. How hard you work will be based on the testing we do together and how you feel each day you come into the clinic".*

13

Education about benefits of HIIT

- Discuss physical and mental benefits of HIIT.
- Link benefits to goals of the client.
  - For example, cardiorespiratory fitness linked to reduced stroke risk.
  - For example, neurological benefits to assist with recovery.
- Must be **personalised** to each client.
  - One-on-one discussion.

14

Education about safety/monitoring during HIIT

- Discuss methods to ensure safety to increase client confidence.
  - Medical clearance, screening/assessment.
  - Protocol (e.g., intensity and duration), modality.
  - Monitoring.
- Discussion of risk versus benefit.
  - For example, *"You may feel a little tired, hot and sweaty during the exercise, but this type of exercise will help your heart and brain work better the more we do this".*
- Add additional safety/monitoring measures if desired/needed by the client.
  - For example, safety railing, fatigue VAS, dyspnoea scale.

15

Chapter 13 Research Portfolio Appendix

Ashcroft, S. K., Ironside, D. D., Johnson, L., Kuys, S. S., & Thompson-Butel, A. G. (2022). Effect of exercise on Brain-Derived Neurotrophic Factor in stroke survivors: A systematic review and meta-analysis. *Stroke*, *53*(12), 3706–3716. https://doi.org/10.1161/STROKEAHA.122.039919

Statement of contribution of others

Contributor	Statement of contribution	Signature
Ashcroft, Sarah K. (Candidate)	Project design (70%) Data analysis (70%) Manuscript preparation (70%)	I acknowledge that my contribution to the above paper is 70% percent.
Ironside, Daniel D.	Data analysis (25%) Manuscript preparation (5%)	I acknowledge that my contribution to this paper is as stated.
Johnson, Liam	Project design (10%) Manuscript preparation (8%)	I acknowledge that my contribution to this paper is as stated.
Kuys, Suzanne S.	Project design (10%) Manuscript preparation (8%)	I acknowledge that my contribution to this paper is as stated.
Thompson-Butel, Angelica G.	Project design (10%) Data analysis (5%) Manuscript preparation (8%)	I acknowledge that my contribution to this paper is as stated.

Systematic review and meta-analysis as published in Stroke

Title: The effect of exercise on Brain-Derived Neurotrophic Factor (BDNF) in stroke survivors: A systematic review and meta-analysis.

Authors: Ashcroft Sarah K (MCEP)[1], Ironside Daniel D (BExSc Hon)[1], Johnson Liam (PhD)[2,3], Kuys Suzanne S (PhD)[4] and Thompson-Butel Angelica G (PhD)[1]

Affiliations:

[1] School of Behavioural and Health Sciences, Australian Catholic University, Strathfield, NSW, Australia

[2] School of Behavioural and Health Sciences, Australian Catholic University, Fitzroy, VIC, Australia

[3] Melbourne School of Health Sciences, University of Melbourne, Parkville, VIC, Australia

[4] School of Allied Health, Australian Catholic University, Banyo, QLD, Australia

Short title: BDNF changes following exercise post-stroke.

Corresponding author:

Sarah K Ashcroft

School of Behavioural and Health Sciences

Australian Catholic University

163-167 Albert Road, Strathfield, NSW, 2135, Australia

Email: Sarah.Ashcroft@myacu.edu.au

Twitter: @SarahKAshcroft

Keywords: stroke, brain-derived neurotrophic factor, exercise, rehabilitation, neuroplasticity

Word count:

Introduction to Disclosures	2,425
Abstract	161
Figures:	3
Tables:	2
References:	48

Non-standard Abbreviations and Acronyms

ACSM	American College of Sport Medicine
BDNF	Brain-Derived Neurotrophic Factor
CI	Confidence interval
COG	Cognitive training
HIT/HIIT	High-intensity interval training
HR_{max}	Heart rate maximum
HRR	Heart rate reserve
MD	Mean difference
min	Minute
NA	Not applicable
ng/mL	Nanograms per millilitre
NIHSS	National Institutes of Health Stroke Scale
NR	Not reported
PT	Physiotherapy
RCT	Randomised controlled trial
RM	Repetition maximum
RT	Resistance training
SD	Standard deviation
USA	United States of America
VO_2peak/VO_2max	Maximal oxygen uptake

Abstract

Background. Brain-Derived Neurotrophic Factor (BDNF) is a biomarker of neuroplasticity linked with better functional outcomes after stroke. Early evidence suggests that increased concentrations after exercise may be possible for people with stroke, however it is unclear how exercise parameters influence BDNF concentration. *Methods.* This systematic review and meta-analysis searched seven electronic databases. Experimental or observational studies measuring changes in BDNF concentration after exercise in people post-stroke were included. Data were extracted including characteristics of the study, participants, interventions, and outcomes. Several fixed and random effects meta-analyses were completed. *Results.* Seventeen studies including a total of 687 participants met the eligibility criteria (six randomised trials). Significant improvements were observed in BDNF concentration following a single session (mean difference [MD] 2.49 ng/mL, 95% CI 1.10 to 3.88) and program of high intensity aerobic exercise (MD 3.42 ng/mL, 95% CI 1.92 to 4.92). *Conclusions.* High intensity aerobic exercise can increase circulating BDNF concentrations, which may contribute to increased neuroplasticity.
Registration. PROSPERO registration CRD42021251083.

1. Introduction

Stroke is the third leading cause of death and mortality combined worldwide.[1] Stroke survivors experience impaired movement and function,[2] often resulting in reduced physical fitness compared to healthy populations.[3] Multidisciplinary rehabilitation, including aerobic exercise, is recommended to optimise recovery and functional improvements following stroke.[4] Aerobic exercise aids motor learning, and relearning and is mediated by neuroplasticity.[5]

Brain-Derived Neurotrophic Factor (BDNF) is a biomarker of neuroplasticity associated with stroke prognosis and recovery.[6] BDNF is upregulated in response to changes in energy use within the body, with greater concentrations of BDNF demonstrated following exercise.[7] A meta-analysis demonstrated a program of aerobic exercise increased BDNF concentration, but only one study examined stroke survivors, and non-aerobic exercise interventions were excluded.[8] While another demonstrated acute effects of physical training on BDNF concentration,[9] it remains unclear how exercise training parameters (i.e. intensity, mode)

influence BDNF concentration post-stroke. There is currently no systematic review demonstrating the effects of resistance training on BDNF concentration post-stroke, and studies have produced variable results in healthy adults.[10] Pre-clinical findings suggest moderate to high intensity aerobic exercise increases BDNF concentration in rat stroke models,[3] but whether this, or other exercise training, similarly increase BDNF in humans is unclear. Given the potential link between exercise, BDNF concentration and stroke recovery,[11] a clearer understanding of the optimal exercise prescription to increase BDNF concentration is necessary. This review aims to identify the intensity and duration of exercise required to produce increases in BDNF concentration post-stroke.

2. Methods

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[12] and is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021251083).

2.1. *Literature Search*

The APA Thesaurus of Psychological Index Terms, CINAHL, Embase Classic + Embase, Medline, PubMed, SportDiscus and Web of Science Core Collection electronic databases were searched from inception until January 31st, 2022. The following umbrella search terms were used: *stroke, exercise, and brain-derived neurotrophic factor*. Full search strategies are found in Table S1. Reference lists of included studies were screened for relevant studies.

2.2. *Eligibility Criteria*

Retrieved searches were downloaded and duplicates were manually removed in EndNote (https://endnote.com/). All screening was completed using Covidence (https://www.covidence.org/), by two reviewers (SKA and DDI) independently. Full-text articles were screened using the following inclusion criteria: (1) human study (≥18 years), (2) diagnosis of stroke, (3) delivery of an exercise intervention of any modality, (4) measurement of blood-derived BDNF concentration and (5) experimental or observational study. Disagreements between reviewers were moderated by a third independent assessor (ATB) until consensus was reached.

2.3. Methodological Quality Assessment

To assess the risk of bias of included randomised trials, the Revised Cochrane Risk-of-Bias Tool for Randomised Interventions (RoB 2)[13] was used. To assess the risk of bias of included non-randomised trials, the Risk of Bias in Non-Randomised Studies – of Interventions (ROBINS-I)[14] was used. Two independent assessors implemented these criteria (SKA and DDI), with disagreements moderated by a third independent assessor (ATB). The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[15] to identify the certainty of evidence was completed by one assessor (SKA) and reviewed by the co-authors.

2.4. *Data Extraction and Synthesis*

Data were extracted by a single reviewer (SKA) and validated by a second reviewer (DDI). Extracted study data included: study, participant, intervention, and comparison group characteristics (if applicable) and outcome measures, including BDNF analysis method and concentration. Missing data were sought from study authors via email. If no response was received despite follow up, the missing information was described as not reported. Participant information was collated and mean ± standard deviation (SD) or frequency (percentage) was determined. The exercise intervention was categorised as 'low', 'moderate' and 'high' intensity as outlined by the American College of Sport Medicine (ACSM)[16] for consistency with previous literature.[3] BDNF concentrations were converted to ng/mL if not originally reported in this measurement unit.

2.5. Meta-analysis

A meta-analysis was planned based on the following criteria, included studies were: (1) clinically homogenous, and (2) statistically homogenous determined using a Chi squared test (I^2). A fixed-effects model was used for studies considered highly homogenous (I^2 <60%).[17] A random-effects model was used for studies considered highly heterogenous (I^2 ≥60%).[17] Meta-analysis results were reported as mean differences (MD) and 95% confidence intervals (CI). Effect size was reported using a Z score and described in accordance with established cut-offs.[18] All meta-analyses were conducted using the Cochrane Review Manager software, RevMan version. 5.4 (http://ims.cochrane.org/revman/download).

3. Results

The data that support the findings of this study are available from the corresponding author upon reasonable request.

3.1. Included Studies

The literature search yielded a total of 2,195 articles, of which 1,489 were screened for eligibility (Figure 1). Following title and abstract screening, 43 full-text articles were screened. Twelve additional full-text articles were screened following a hand search of included studies reference lists. Full-text screening excluded 37 studies as they did not satisfy the inclusion criteria. Thus 17 studies were included for analysis (Figure 1).[19-35]

Of the 17 studies, six (35%) were randomised trials,[24, 27, 28, 32, 33, 35] one (6%) was a pseudo-randomised trial,[31] and the remaining ten (59%) were non-randomised studies[19-23, 25, 26, 29, 30, 34] (Table 1).

A total of 687 participants were included, 418 (61%) males and 259 (38%) females. Participant sex was not reported in one group in one study (n = 10, 1% of total included participants).[34] Five (29%) studies targeted ischaemic stroke[23-25, 30, 33] and the remaining twelve (71%) included all stroke. Mean ± SD age of participants was 58 ± 5 years (range, 28-81 years). Of the 17 studies, four (24%) targeted acute (1-7 days) stroke[20, 22, 30, 33] and five (29%) targeted chronic (>6 months) stroke,[19, 21, 26, 31, 34] with the remaining eight studies (47%) targeting any time post-stroke. Mean ± SD time post-stroke was 47 ± 36 months (range, 24 hours – 9.2 years).

A total of 37 exercise interventions were provided and BDNF concentration were calculated at various timepoints (Table 2).

3.2. BDNF Concentration Reporting

Sixteen studies (94%) analysed serum and one (6%) study analysed plasma (34). Fourteen (82%) studies used the Enzyme-Linked Immunosorbent Assay (ELISA),[19-27, 29, 31-33, 35] one (6%) used the MAGPIX Multiplex Analyser[30] and one (6%) used the Human BDNF Emax

ImmunoAssay.[34] One (6%) study reported BDNF analysis was outsourced to an external facility.[28]

Pre- and post-intervention BDNF concentrations were reported for 26 of the 37 included interventions. The change in BDNF concentration were reported for seven interventions,[19, 21] only the significance of the change was reported for three interventions[24] and no results were reported for one intervention.[34] Individual participant BDNF concentrations were provided for seven interventions.[19, 21]

3.3. Intervention Characteristics

3.3.1. Frequency

The duration of exercise programs ranged from one to 26 weeks, with a mean ± SD of 24 ± 16 sessions (range, 2-78 sessions). The frequency of sessions within the programs of exercise ranged from twice per week to daily.

3.3.2. Intensity

Exercise intensity was reported as measure of heart rate in seven studies.[19, 21, 23, 26, 31, 34, 35] Volume of maximal/peak oxygen uptake was used in five studies.[19, 27-29, 32] Percentage of comfortable walking speed was utilised in one study.[21] Two studies prescribed resistance exercise using the absolute value or a percentage of the number of repetitions successfully completed by the participant.[24, 34] Ten of the 37 exercise interventions did not report exercise intensity.[20, 21, 25, 30, 32, 33, 35]

Using the ACSM aerobic exercise intensity cut-offs (Table S2) (16), four interventions were 'low-intensity',[21, 23, 26, 28] four were 'moderate-intensity',[19, 23, 27, 28] and fifteen were 'high-intensity'.[19, 21, 26-29, 31, 32, 34, 35] Fifteen interventions utilised non-aerobic modalities, therefore intensity was unable to be classified.[20, 22, 24-26, 30, 32-35]

3.3.3. Time

The mean ± SD duration of each exercise session in the included studies was 59 ± 48 min. Single-session interventions (27 ± 11 min) were shorter than multi-session programs (74 ± 52 min).

3.3.4. Modality

Aerobic exercise was utilised in 22 of the 37 interventions,[19, 21, 23, 25-29, 31, 32, 34, 35] while non-aerobic interventions were utilised in 15 interventions.[20, 22, 24-26, 30, 32-35]

3.4. Methodological Quality

Of the six randomised trials, two (33%) were assessed as a 'Low' risk of bias,[32, 35] while four (67%) had 'Some Concerns'[24, 27, 28, 33] (Table S3). Of the 11 non-randomised trials, nine (82%) were assessed as a 'Low' risk of bias,[19, 21-23, 25, 26, 29-31] and two (18%) were assessed as 'Moderate'[20, 34] (Table S4).

3.5. Effect of a Single Session of Exercise

Eleven interventions provided a single session of aerobic exercise.[19, 21, 23, 29, 31]

3.5.1. Single Session of Low Intensity Aerobic Exercise

Two interventions used low intensity aerobic exercise,[21, 23] demonstrating a decrease in BDNF concentration (range -2.36 to -0.0375 ng/mL). A meta-analysis (Figure 2A, 2.1.1) shows a small, non-significant effect, which favours no exercise (MD -0.04, 95% CI -0.30 to 0.22, p = 0.76), with low heterogeneity and high certainty (Table S5).

3.5.2. Single Session of Moderate Intensity Aerobic Exercise

Two interventions used moderate intensity aerobic exercise,[19, 23] demonstrating mixed effects on BDNF concentration (range -0.492 to 0.0448 ng/mL). A meta-analysis (Figure 2A, 2.1.2) shows a small, non-significant effect, which favours exercise (MD 0.04, 95% CI -0.21 to 0.30, p = 0.73), with low heterogeneity and high certainty (Table S5).

3.5.3. Single Session of High Intensity Aerobic Exercise

Seven interventions used high intensity aerobic exercise,[19, 21, 29, 31] demonstrating mixed effects on BDNF concentration (range -1.65 to 4.761 ng/mL) with larger increases demonstrated following maximal efforts[19, 29] and high intensity interval training.[19] A meta-analysis (Figure 2A, 2.1.3) shows a very large, statistically significant effect, which favours exercise (MD 2.49, 95% CI 1.10 to 3.88, p = 0.0005), with low heterogeneity and high certainty (Table S5).

3.6. Effect of a Program of Exercise

Twenty-six intervention programs were utilised, 11 aerobic[25-28, 32, 34, 35] and 15 non-aerobic.[20, 22, 24-26, 30, 32-35]

3.6.1. Effect of a Program of Aerobic Exercise

Two interventions were omitted from meta-analysis because the intensity of exercise[25] and BDNF concentration[34] were not reported. One intervention increased the intensity of exercise from 'moderate' to 'high' mid-program.[26] This program was analysed as two separate interventions. Therefore, a total of 10 interventions were analysed.

3.6.1.1. Program of Low Intensity Aerobic Exercise

One program of low intensity aerobic exercise demonstrated an increase in BDNF concentration.[28] This result shows a medium, statistically non-significant effect, which favours exercise (MD 0.77, 95% CI -0.83 to 2.38, p = 0.35).

3.6.1.2. Program of Moderate Intensity Aerobic Exercise

Three interventions provided a program of moderate intensity aerobic exercise,[26-28] demonstrating mixed effects on BDNF concentration (range -5.499 to 1.927 ng/mL). A meta-analysis (Figure 2B) shows a small, statistically non-significant effect, which favours no exercise (MD -0.22, 95% CI -3.31 to 2.88, p = 0.89), with considerable heterogeneity and low certainty (Table S5).

3.6.1.3. Program of High Intensity Aerobic Exercise

Six interventions provided a high intensity exercise program,[26-28, 32, 35] demonstrating mixed effects on BDNF concentration (range -3.7 to 4.60 ng/mL). A meta-analysis (Figure 2C) shows a very large, statistically significant effect, which favours exercise (MD 3.42, 95% CI 1.92 to 4.92, p = 0.00), with low heterogeneity and high certainty (Table S5).

3.6.2. Effect of a Program of Non-Aerobic Exercise

Fifteen interventions included non-aerobic exercise,[20, 22, 24-26, 30, 32-35] demonstrating mixed effects on BDNF concentration (range -4.7 to 3.72 ng/mL). Twelve interventions were included for meta-analysis (Figure 3). Results show a medium, non-significant effect, which

favours exercise (MD 0.72, 95% CI -0.05 to 1.50, p = 0.07), with considerable heterogeneity and low certainty (Table S5).

4. Discussion

This systematic review and meta-analysis demonstrates that exercise can increase BDNF concentration from rest, however, exercise intensity appears to be a critical factor. Our results demonstrate larger increases in BDNF concentration following high intensity aerobic exercise. Increases in BDNF, though smaller and non-significant, were also evident following a program of non-aerobic exercise.

Our results support aerobic exercise as a preferred mode of exercise to optimally increase BDNF concentrations within post-stroke human adults. We demonstrated that a single session and a program of high intensity aerobic exercise can elicit significant increases in BDNF concentration. Our results are consistent with existing evidence of aerobic exercise increasing BDNF concentrations in people with stroke.[8] Our results also support the suggestion that programs of aerobic exercise may produce more sustained increases in BDNF concentration.[36] We identified larger mean differences in BDNF concentrations after a high intensity aerobic exercise compared to low or moderate intensities. This is a first time finding for this population but is consistent with observations in healthy young adults[37] and suggests exercise intensity is critical to the magnitude of change in BDNF concentration. While the exact mechanisms are unclear, larger increases in BDNF concentration associated with high intensity aerobic exercise may be attributed to upregulated cell metabolism.[38] This upregulation is linked with the pathway by which BDNF expression is mediated, with subsequent increased BDNF synthesis and release into the bloodstream.[39]

4.1 Limitations

Few RCTs were included and the omission of relevant intervention and/or outcome measure information reduced the quality of the included studies. Most studies were not adequately powered to detect BDNF concentration changes, and between-study heterogeneity may impact conclusions drawn. This heterogeneity may be associated with participant differences, such as stroke severity or age, as BDNF concentration is negatively correlated with National Institutes of Health Stroke Scale (NIHSS) scores[40] and increasing age.[41]

However, this heterogeneity may assist in the clinical application of our results where stroke cohorts are not homogenous.

4.2 Future directions

Future studies should comply with the Stroke Recovery and Rehabilitation Roundtable (SRRR) recommendations for the development, monitoring, and reporting of stroke rehabilitation research.[42] Standardised stroke descriptors such as NIHSS score[43] or TOAST criteria[44] are required to allow greater generalisability. Greater detail regarding the classification of participant age (e.g., older (>40 years) or younger (<40 years)) is required to improve BDNF concentration interpretation.[45] Interventions should be reported in accordance with the Template for Intervention Description and Replication (TIDieR) checklist and guide,[46] including any personalisation and fidelity of the interventions[42] to allow for reproducibility. High intensity aerobic exercise in close temporal proximity to other therapies may optimise motor re-learning and functional improvements post-stroke.[47] However, future studies must explore the optimal dose and ordering of this combined therapy.

5. Conclusions

This systematic review suggests that both a single session, and program, of high intensity aerobic exercise increases BDNF concentration. While aerobic exercise is currently recommended as a part of multidisciplinary rehabilitation to promote cardiovascular benefits, high intensity aerobic exercise shows promise as an intervention that may enhance circulating BDNF.

6. Acknowledgements

We thank Megan Willis for her statistical advice.

7. Funding Sources

None.

8. Disclosures

None.

9. List of Supplemental Material

Tables S1, S2, S3, S4 and S5

10. References

1. Stark BA, Roth GA, Adebayo OM, Akbarpour S, Aljunid SM, Alvis-Guzman N, Ansar A, Antonazzo IC, Ärnlöv J, Artanti KD et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurology. 2021;20:795-820.
2. Molle Da Costa RD, Luvizutto GJ, Martins LG, Thomaz De Souza J, Regina Da Silva T, Alvarez Sartor LC, Winckler FC, Modolo GP, Molle ERDSD, Dos Anjos SM et al. Clinical factors associated with the development of nonuse learned after stroke: A prospective study. Topics in Stroke Rehabilitation. 2019;26:511-517.
3. Ploughman M, & Kelly LP. Four birds with one stone? Reparative, neuroplastic, cardiorespiratory, and metabolic benefits of aerobic exercise poststroke. Current Opinion in Neurology. 2016;29:684-692.
4. Cassidy JM, & Cramer SC. Spontaneous and therapeutic-induced mechanisms of functional recovery after stroke. Translational Stroke Research. 2016;8:33-46.
5. Quaney BM, Boyd LA, McDowd JM, Zahner LH, Jianghua H, Mayo MS, & Macko RF. Aerobic exercise improves cognition and motor function poststroke. Neurorehabilitation and Neural Repair. 2009;23:879-885.
6. Schabitz WR, Steigleder T, Cooper-Kuhn CM, Schwab S, Sommer C, Schneider A, & Kuhn HG. (2007). Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis. Stroke. 2007;38:2165-2172.
7. Marosi K, & Mattson MP. BDNF mediates adaptive brain and body responses to energetic challenges. Trends in Endocrinology and Metabolism. 2013;25:89-98.
8. Mackay CP, Kuys SS, & Brauer SG. The effect of aerobic exercise on brain-derived neurotrophic factor in people with neurological disorders: A systematic review and meta-analysis. Neural Plasticity. 2017:4716197-4716199.
9. Mojtabavi H, Shaka Z, Momtazmanesh S, Ajdari A, & Rezaei N. Circulating brain-derived neurotrophic factor as a potential biomarker in stroke: A systematic review and meta-analysis. Journal of Translational Medicine. 2022;20:126-126.

10. Arazi H, Babaei P, Moghimi M, Asadi A. Acute effects of strength and endurance exercise on serum BDNF and IGF-1 levels in older men. BMC Geriatrics. 2021;21:50-50.
11. Liu W, Wang X, O'Connor M, Wang G, & Han F. Brain-derived neurotrophic factor and its potential therapeutic role in stroke comorbidities. Neural Plasticity. 2020;2020:1969482-1969413.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71-n71.
13. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898-l4898.
14. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919-i4919.
15. Brozek JL, Akl EA, Guyatt GH, Schünemann HJ, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, Phillips B, Lelgemann M, Lethaby A, & Bousquet J. Grading quality of evidence and strength of recommendations in clinical practice guidelines Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy (Copenhagen). 2009;64:669–677.
16. Pescatello LS. (2014). General principles of exercise prescription. In LS Pescatello, R Arena, D Riebe, & PD Thompson (Eds.), ACSM's guidelines for exercise testing and prescription (Ninth ed., pp. 162-193). Lippincott Williams & Wilkins.
17. McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, & Johnston RV. Chapter 9: Summarizing study characteristics and preparing for synthesis. Cochrane. 2021. https://training.cochrane.org/handbook/current/chapter-09
18. Zlowodzki M, Poolman RW, Kerkhoffs GM, Tornetta P Bhandari M, & On behalf of the International Evidence-Based Orthopedic Surgery Working Group. (2007). How to interpret a meta-analysis and judge its value as a guide for clinical practice. Acta Orthopaedica. 2007;78:598-609.
19. Boyne P, Meyrose C, Westover J, Whitesel D, Hatter K, Reisman DS, Carl D, Khoury JS, Gerson M, Kissela B, & Dunning K. Effects of exercise intensity on acute circulating

molecular responses post-stroke. Neurorehabilitation and Neural Repair. 2020;34:222-234.

20. Chang WH, Shin MA, Lee A, Kim H, & Kim YH. Relationship between serum BDNF levels and depressive mood in subacute stroke patients: A preliminary study. International Journal of Molecular Sciences. 2018;19:3131.
21. Charalambous CC, Alcantara CC, French MA, Li X, Matt KS, Kim HE, Morton SM, & Reisman DS. A single exercise bout and locomotor learning after stroke: Physiological, behavioural, and computational outcomes. The Journal of Physiology. 2018;596:1999-2016.
22. Chaturvedi P, Singh A, Tiwari V, & Thacker A. Post-stroke BDNF concentration changes following proprioceptive neuromuscular facilitation (PNF) exercises. Journal of Family Medicine and Primary Care. 2020;9:3361-3369.
23. de Morais VAC, Tourino MFDS, Almeida ACDS, Albuquerque TBD, Linhares RC, Christo PP, Martinelli PM, & Scalzo PL. A single session of moderate intensity walking increases brain-derived neurotrophic factor (BDNF) in the chronic post-stroke patients. Topics in Stroke Rehabilitation. 2018;25:1-5.
24. Du X, Chen W, Zhang N, Bian X, & Yu W. The effects of low-intensity resistance training with or without blood flow restriction on serum BDNF, VGEF and perception in patients with post-stroke depression Neuroendocrinology Letter. 2021;42:229-235.
25. El-Tamawy MS, Abd-Allah F, Ahmed SM, Darwish MH, & Khalifa HA. Aerobic exercises enhance cognitive functions and brain derived neurotrophic factor in ischemic stroke patients. NeuroRehabilitation (Reading, Mass.). 2014;34:209-213.
26. Harnish SM, Rodriguez AD, Blackett DS, Gregory C, Seeds L, Boatright JH, & Crosson B. Aerobic exercise as an adjuvant to aphasia therapy: theory, preliminary findings, and future directions. Clinical Therapeutics. 2018;40:35-48.
27. Hsu CC, Fu TC, Huang SC, Chen CPC, & Wang JS. Increased serum brain-derived neurotrophic factor with high-intensity interval training in stroke patients: A randomized controlled trial. Annals of Physical and Rehabilitation Medicine. 2021;64:101385-101385.
28. Kim TG, Bae SH, & Kim KY. Effects of dual-task training with different intensity of aerobic exercise on cognitive function and neurotrophic factors in chronic stroke patients. Research Journal of Pharmacy and Technology. 2019;12:693-698.

29. King M, Kelly LP, Wallack EM, Hasan SMM, Kirkland MC, Curtis ME, Chatterjee T, McCarthy J, & Ploughman M. Serum levels of insulin-like growth factor-1 and brain-derived neurotrophic factor as potential recovery biomarkers in stroke. Neurological Research. 2019;41:354-363
30. Koroleva ES., Tolmachev IV, Alifirova VM, Boiko AS, Levchuk LA, Loonen AJM, & Ivanova SA. Serum BDNF's role as a biomarker for motor training in the context of ar-based rehabilitation after ischemic stroke. Brain Sciences. 2020;10:623.
31. Mackay CP, Brauer SG, Kuys SS, Schaumberg MA, & Leow LA. The acute effects of aerobic exercise on sensorimotor adaptation in chronic stroke. Restorative Neurology and Neuroscience. 2021;39:367-377.
32. Ploughman M, Eskes GA, Kelly LP, Kirkland MC, Devasahayam AJ, Wallack EM, Abraha B, Hasan SMM, Downer MB, Keeler L. et al. Synergistic benefits of combined aerobic and cognitive training on fluid intelligence and the role of IGF-1 in chronic stroke. Neurorehabilitation and Neural Repair. 2019;33:199-212.
33. Rahayu UB, Wibowo S, Setyopranoto I, & Romli MH. Effectiveness of physiotherapy interventions in brain plasticity, balance and functional ability in stroke survivors: A randomized controlled trial. NeuroRehabilitation (Reading, Mass.). 2020;47:463-470.
34. Ryan AS, Xu H, Ivey FM, Macko RF, & Hafer-Macko CE. Brain-derived neurotrophic factor, epigenetics in stroke skeletal muscle, and exercise training. Neurology. Genetics. 2019;5:e331-e331
35. Valkenborghs SR, Vliet P, Nilsson M, Zalewska K, Visser MM, Erickson KI, & Callister R. Aerobic exercise and consecutive task-specific training (AExaCTT) for upper limb recovery after stroke: A randomized controlled pilot study. Physiotherapy Research International. 2019;24:e1775.
36. Griffin ÉW, Mullally S, Foley C, Warmington SA, O'Mara SM, & Kelly ÁM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. Physiology and Behavior. 2011;104:934-941.
37. Fernández-Rodríguez R, Álvarez-Bueno C, Martínez-Ortega IA, Martínez-Vizcaíno V, Mesas AE, & Notario-Pacheco B. Immediate effect of high-intensity exercise on brain-derived neurotrophic factor in healthy young adults: A systematic review and meta-analysis. Journal of Sport and Health Science. 2021;11:367-375.

38. Brandt N, Dethlefsen MM, Bangsbo J, & Pilegaard H. PGC-1α and exercise intensity dependent adaptations in mouse skeletal muscle. PloS One. 2017;12:e0185993-e0185993.
39. El Hayek L, Khalifeh M, Zibara V, Abi Assaad R, Emmanuel N, Karnib N, El-Ghandour R, Nasrallah P, Bilen M, Ibrahim P, Younes J, Abou Haidar E, Barmo N, Jabre V, Stephan JS, & Sleiman SF. Lactate mediates the effects of exercise on learning and memory through sirt1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). The Journal of Neuroscience. 2019;39:2369-2382.
40. Qiao HJ, Li ZZ, Wang LM, Sun W, Yu JC, & Wang B. Association of lower serum Brain-derived neurotrophic factor levels with larger infarct volumes in acute ischemic stroke. Journal of Neuroimmunology. 2017;307:69-73.
41. Lasek-Bal A, Jędrzejowska-Szypułka H, Różycka J, Bal W, Holecki M, Duława J, & Lewin-Kowalik J. Low concentration of BDNF in the acute phase of ischemic stroke as a factor in poor prognosis in terms of functional status of patients. Medical Science Monitor, 2015;21:3900-3905.
42. Walker MF, Hoffmann TC, Brady MC, Dean CM, Eng JJ, Farrin AJ, Felix C, Forster A, Langhorne P, Lynch EA et al. Improving the development, monitoring and reporting of stroke rehabilitation research: consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. Neurorehabilitation and Neural Repair. 2017;31:877.
43. Amalia L, & Dalimonthe NZ. Clinical significance of platelet-to-white blood cell ratio (PWR) and National Institute of Health stroke scale (NIHSS) in acute ischemic stroke. Heliyon. 2020;6:e05033-e05033
44. Adams JHP, Bendixen BH, Kappelle JL, Biller J, Love BB, Gordon DL, & Marsh REE. Classification of subtype of acute ischemic stroke: Definitions for use in a multicenter clinical trial: TOAST. Trial of Org 10172 in acute stroke treatment. Stroke. 1993;24:35-41.
45. George MG. Risk Factors for Ischemic Stroke in Younger Adults. Stroke. 2020;51:729–735
46. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, Altman DG, Barbour V, Macdonald H, Johnston M, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ (Online). 2014;348:g1687-g1687.

47. Thomas R, Flindtgaard M, Skriver K, Geertsen SS, Christiansen L, Korsgaard Johnsen L, Busk DVP, Bojsen-Møller E, Madsen MJ, Ritz C. et al. Acute exercise and motor memory consolidation: Does exercise type play a role? Scandinavian Journal of Medicine & Science in Sports. 2017;27:1523-1532.
48. Borg G. Perceived exertion as an indicator of somatic stress. Scandinavian Journal of Rehabilitation and Medicine. 1970;2:92-98.

11. Tables

Table 1. Characteristics of participants

Study	Country	Study type	Stroke type	Stroke severity (NIHSS) (mean ± SD)	Number of participants (number of females)	Time post-stroke (months) (mean ± SD)	Age (years) (mean ± SD)
Boyne et al., 2020[19]	USA	Cohort study	Ischaemic or Haemorrhagic	NR	16 (7)	78.1 ± 49.2	57.4 ± 9.7
Chang et al., 2018[20]	Korea	Cohort study	Ischaemic or Haemorrhagic	7.5 ± 5.4	38 (15)	0.52 ± 0.20	62.9 ± 14.6
Charalambous et al., 2018[21]	USA	Cohort study	Ischaemic or Haemorrhagic	NR	37 (14)	67.9 ± 60.4	58.0 ± 12.0
Chaturvedi et al., 2020[22]	India	Prospective cohort study	Ischaemic or Haemorrhagic	Mild (1-4): n = 17 Moderate (5-14): n = 60 Severe (15-25): n = 7	208 (82)	0-0.49	55.3 ± 11.1
de Morais et al., 2018[23]	Brazil	Cohort study	Ischaemic	NR	10 (5)	110.5 ± 69.6	58 ± 12.8
Du et al., 2021[24]	China	Randomised trial	Ischaemic	NR	24 (10)	1.46 ± 0.13	47.8 ± 4.8

El-Tamawy et al., 2014[25]	Egypt	Cohort study	Ischaemic	NR	30 (9)	3-18	48.4 ± 6.4
Harnish et al., 2018[26]	USA	Cohort study	Ischaemic or Haemorrhagic	NR	12 (5)	56.4 ± 39.6	57.9 ± 14.4
Hsu et al., 2021[27]	Taiwan	RCT	Ischaemic or Haemorrhagic	NR	23 (3)	>24	55.8 ± 3.82
Kim et al., 2019[28]	Korea	Randomised trial	Ischaemic or Haemorrhagic	NR	27 (13)	14.9 ± 0.3	58.5 ± 1.1
King et al., 2019[29]	Canada	Cohort study	Ischaemic or Haemorrhagic	4.3 ± 4.4	35 (12)	31.5 ± 26.7	65.2 ± 9.4
Koroleva et al., 2020[30]	Russia	Cohort study	Ischaemic	NR	50 (28)	0-2.96	64.0 ± 1.7 m (IQR): A-Rehab: 62 (57;67) B-Rehab: 65.5 (60;68)
Mackay et al., 2021[31]	Australia	Pseudo-randomised trial	Ischaemic or Haemorrhagic	NR	20 (5)	47	60 ± 14
Ploughman et al., 2019[32]	Canada	Block-randomised, single-blinded pilot trial	Ischaemic or Haemorrhagic	Aerobic + COG: 5.5 ± 3.5	52 (16)	41 ± 39.8	63.4 ± 11.3

				Aerobic + Games: 4.2 ± 4.2 Activity + COG: 5.5 ± 5.3 Activity + Games: 4.4 ± 3.3			
Rahayu et al., 2020[33]	Indonesia	Parallel two-arm RCT	Ischaemic	NR	64 (28)	0.03	59.4 ± 0.8
Ryan et al., 2019[34]	USA	Longitudinal study	Ischaemic or Haemorrhagic	NR	21 (4)	84	43-81
Valkenborghs et al., 2019[35]	Australia	Pilot RCT	Ischaemic or Haemorrhagic	NR	20 (9)	71.7 ± 91.2	55.4 ± 16

Abbreviations – NIHSS: National Institutes of Health Stroke Scale; SD: Standard deviation; USA: United States of America; NR: Not reported; RCT: Randomised controlled trial; m (IQR): Median (Interquartile range); COG: Cognitive training

Table 2. Interventions and outcome measures

Study	Groups	Frequency	Intensity	ACSM intensity classification	Duration (min)	Modality	Measure timepoints	BDNF change (ng/mL)
				Single session				
Boyne et al., 2020[19]	Symptom-limited GXT	Single session	Maximal effort	High	As long as tolerated	Treadmill	Rest & post-exercise	↑ 4.62 ± 6.14
	MCT-Tread	Single session	45±5% HRR	Moderate	25	Treadmill	Rest & post-exercise	↓ 0.49 ± 3.98
	HIT-Tread	Single session	>60% HRR	High	25	Treadmill	Rest & post-exercise	↑ 3.44 ± 5.95
	HIT-Stepper	Single session	>60% HRR	High	25	Stepper	Rest & post-exercise	↑ 1.59 ± 7.71
Charalambous et al., 2018[21]	Control	Single session	25% comfortable walking speed	Low	20	Treadmill & Split-belt	Rest & post-exercise	↓ 2.35 ± 13.93

	Treadmill Walking	Single session	70-85% age-predicted HR_{max}	High	20	Treadmill & Split-belt	Rest & post-exercise	↓ 1.66 ± 7.14
	Total Body Ergometer	Single session	70-85% age-predicted HR_{max}	High	20	Total Body Ergometer	Rest & post-exercise	↓ 1.63 ± 10.05
De Morais et al., 2018[23]	Session 1	Single session	50-63% HR_{max}	Low	45	Overground walking	Rest & post-exercise	↓ 0.038
	Session 2	Single session	64-74% HR_{max}	Moderate	45	Overground walking	Rest & post-exercise	↑ 0.045
King et al., 2019[29]	GXT	Single session	Maximal effort	High	12.46 ± 6.4	Treadmill	Rest & post-exercise	↑ 2.99
Mackay et al., 2021[31]	Moderate-high intensity	Single session	65% HRR	High	30	Treadmill	Rest & post-exercise	↑ 2.99
				Program				
Chang et al., 2018[20]	Standard rehabilitation	2 weeks, PT: 7/week OT: 5/week	NR	NA	PT: 120 OT: 60	PT & OT	Rest, mid-program &	1-week: ↓ 1.24

							post program	2-weeks: ↓ 1.6
Chaturvedi et al., 2020[22]	PNF	2 weeks 5/week	NR	NA	45	PNF	Rest & post program	↑ 3.72
Du et al., 2021[24]	LOW	1 week 2/week	40% 1RM	NA	NR	RT	Rest & post program	NR
	LOW-BFR	1 week 2/week	40% 1RM	NA	NR	RT with BFR cuff on proximal end of moving limb	Rest & post program	NR
	HIGH	1 week 2/week	80% 1RM	NA	NR	Resistance training	Rest & post program	NR
El-Tamawy et al., 2014[25]	Control	8 weeks 3/week	NR	NA	25-30	PT	Rest & post program	↑ 0.18
	Study group	8 weeks 3/week	NR	NA	75-90	PT & Cycling	Rest & post program	↑ 4.65
Harnish et al., 2018[26]	Aerobic + CPNT	8 weeks 3/week	Weeks 1+2: 50% HRR Weeks 3-8: 70% HRR	Weeks 1+2: Moderate Weeks 3-8: High	30	Cycling & CPNT	Rest, mid-program & post program	Pre to mid-program: ↓ 5.50 Mid to post

								program: ↑ 2.59
	Stretching + CPNT	8 weeks 3/week	"Low"	NA	50	Stretching & CPNT	Rest, mid-program & post program	Pre to mid-program: ↑ 2.51 Mid to post program: ↓ 3.61
Hsu et al., 2021[27]	MICT	12-18 weeks 2-3/week	60% VO_{2peak}	Moderate	36	Cycling	Rest & post program	↓ 1.42
	HIIT	12-18 weeks 2-3/week	ON: 80% VO_{2peak} OFF: 40% VO_{2peak}	High	36	Cycling	Rest & post program	↑ 1.85
Kim et al., 2019[28]	Low + Dual-task	6 weeks 5/week	40% VO_{2max}	Low	46.36 ± 3.24	Treadmill & Cognitive tasks	Rest & post program	↑ 0.77
	Moderate + Dual-task	6 weeks 5/week	55% VO_{2max}	Moderate	35.19 ± 2.83	Treadmill & Cognitive tasks	Rest & post program	↑ 1.93
	High + Dual-task	6 weeks 5/week	70% VO_{2max}	High	26.24 ± 3.13	Treadmill & Cognitive tasks	Rest & post program	↑ 4.60

Koroleva et al., 2020[30]	A-Rehab	38 days 7/week	NR	NA	195-207	Air cryotherapy, FES, Manual classic massage, Mechanotherapy, Therapeutic physical culture & Motor rehabilitation using motion sensor and augmented reality	Rest & post program	↑ 0.01
	B-Rehab	10 days 7/week	NR	NA	100	Motor rehabilitation using motion sensor and augmented reality	Rest & post program	↑ 1.01
Ploughman et al., 2019[32]	Aerobic + COG	10 weeks 3/week	Aerobic: 60-80% VO_{2peak} COG: Varied	High	40-60	Treadmill & Computerised dual-n-back training	Rest, post program & 3-month follow-up	Rest to post program: ↓ 3.4

Aerobic + Games	10 weeks 3/week	Aerobic: 60-80% VO_{2peak} Games: NR	High	40-60	Treadmill & Non-adaptive computer-based game	Rest, post program & 3-month follow-up	Rest to post program: ↓ 2.8
Activity + COG	10 weeks 3/week	Activity: NR COG: Varied	NA	40-60	Massage and active/passive ROM exercises on affected side, Functional task training & Computerised dual-n-back training	Rest, post program & 3-month follow-up	Rest to post program: ↑ 1.7
Activity + Games	10 weeks 3/week	Activity: NR Games: NR	NA	40-60	Massage and active/passive ROM exercises on affected side, Functional task training & Non-adaptive computer-based game	Rest, post program & 3-month follow-up	Rest to post program: ↑ 3.1

Rahayu et al., 2020[33]	Neurorestoration intervention	1 week 7/week	Varied	NA	NR	Bobath; PNF; Rood, Carr and Shepherd & CIMT	Rest & post program	↑ 2.62
	Conventional therapy	1 week 7/week	NR	NA	NR	Position change, breathing exercises and exercises in passive and active mobilisation	Rest & post program	↓ 0.68
Ryan et al., 2019[34]	AEX	26 weeks 3/week	60-70% HRR	High	30-50	Treadmill	Rest & post program	NR
	RT	12 weeks 3/week	10-15 RM	NA	NR	RT	Rest & post program	↑ 0.23*
Valkenborghs et al., 2019[35]	AEX + TST	10 weeks 3/week supervised; 3/week unsupervised	Aerobic – ON: 85% HR_{max} OFF: 70% HR_{max} TST: NR	High	90 supervised 60 unsupervised	Cycling & Whole or part-practice upper limb tasks	Rest & post program	↓ 3.7 ± 12.1
	TST	10 weeks 3/week supervised;	NR	NA	90 supervised 60 unsupervised	Whole or part-practice upper limb tasks	Rest & post program	↓ 4.7 ± 14.5

	3/week unsupervised	

Abbreviations – ACSM: American College of Sports Medicine; BDNF: Brain-Derived Neurotrophic Factor; ng/mL: nanograms per millilitre; GXT: Graded exercise test; MCT or MICT: Moderate-intensity continuous training; HRR: Heart rate reserve; HIT or HIIT: High-intensity interval training; HR_{max}: heart rate maximum; PT: Physiotherapy; OT: Occupational therapy; NR: Not reported; NA; Not applicable; PNF: Proprioceptive Neuromuscular Facilitation; RM: Repetition maximum; RT: resistance training; BFR: Blood flow restriction; CPNT: Cued picture-naming treatment; MICT: Moderate-intensity continuous training; VO_2peak or VO_2max: Maximal oxygen uptake; FES: Functional electrical stimulation; COG: Cognitive training; ROM: Range of motion; CIMT: Constraint-Induced Movement Therapy; AEX: Aerobic exercise; TST: Task-specific training

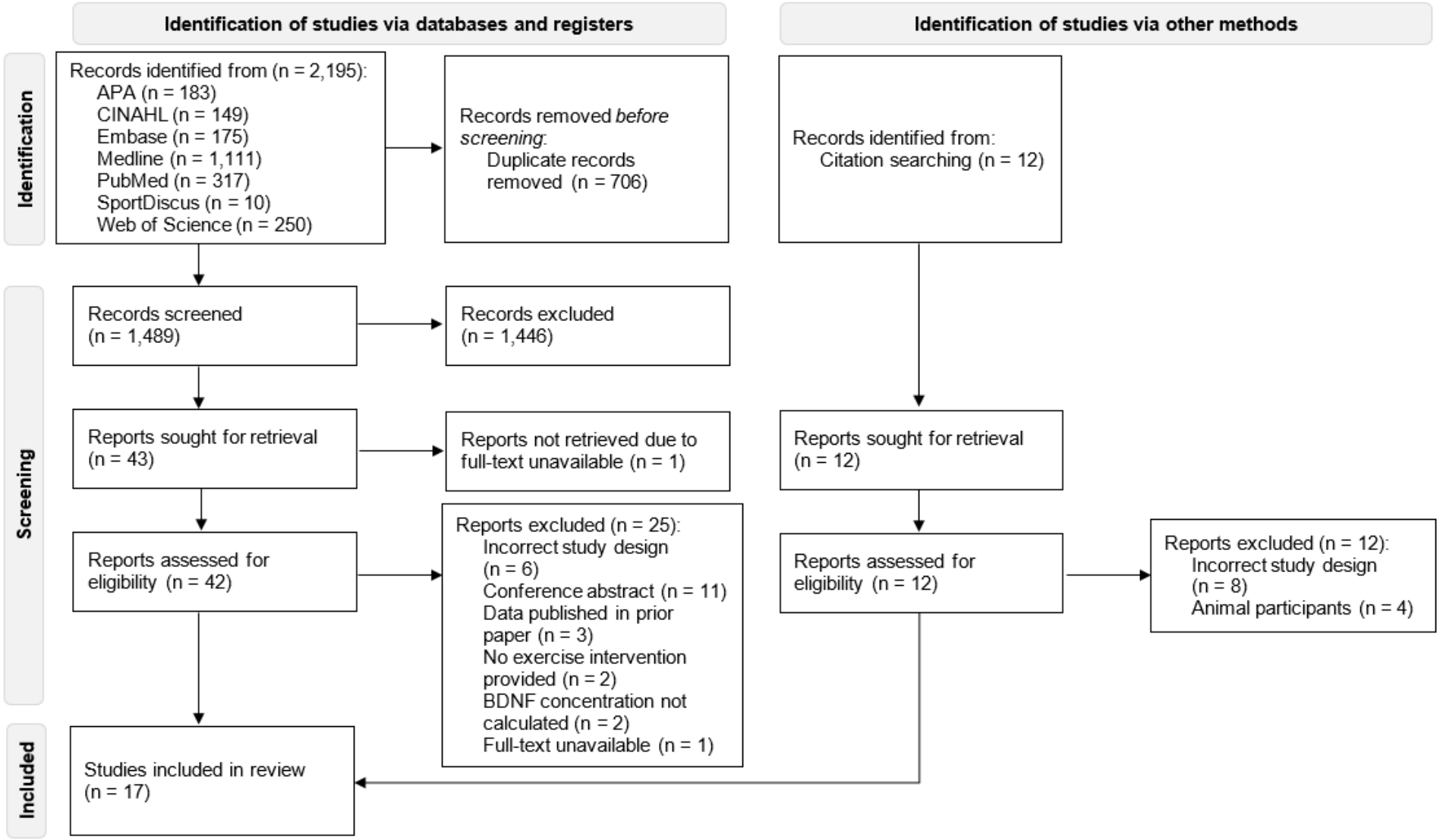
* Plasma-derived BDNF concentration

12. Figure Legends

Figure 1. PRISMA flowchart

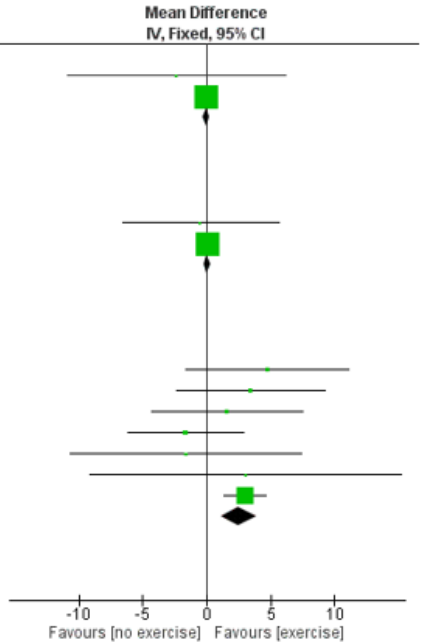
Figure 2. Meta-analysis of aerobic exercise. A: Single session. B: Program of moderate intensity. C: Program of high intensity

Figure 3. Meta-analysis of a program of non-aerobic exercise


Identification of studies via databases and registers
Identification of studies via other methods
Identification
Screening
Included
Records identified from (n = 2,195):
APA (n = 183)
CINAHL (n = 149)
Embase (n = 175)
Medline (n = 1,111)
PubMed (n = 317)
SportDiscus (n = 10)
Web of Science (n = 250)
Records removed *before screening*:
Duplicate records removed (n = 706)
Records identified from:
Citation searching (n = 12)
Records screened (n = 1,489)
Records excluded (n = 1,446)
Reports sought for retrieval (n = 43)
Reports not retrieved due to full-text unavailable (n = 1)
Reports sought for retrieval (n = 12)
Reports assessed for eligibility (n = 42)
Reports excluded (n = 25):
Incorrect study design (n = 6)
Conference abstract (n = 11)
Data published in prior paper (n = 3)
No exercise intervention provided (n = 2)
BDNF concentration not calculated (n = 2)
Full-text unavailable (n = 1)
Reports assessed for eligibility (n = 12)
Reports excluded (n = 12):
Incorrect study design (n = 8)
Animal participants (n = 4)
Studies included in review (n = 17)

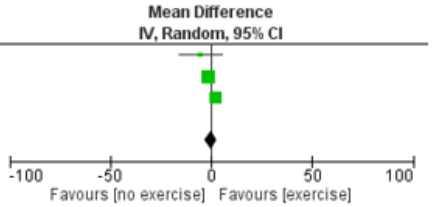
A

Study or Subgroup	Post-exercise Mean	SD	Total	Pre-exercise Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 Single session of low intensity aerobic exercise								
Charalambous 2018	18.13	9.49	13	20.49	12.5	13	0.1%	-2.36 [-10.89, 6.17]
de Morais 2018	1.6542	0.3136	10	1.6917	0.2767	10	99.9%	-0.04 [-0.30, 0.22]
Subtotal (95% CI)			23			23	100.0%	**-0.04 [-0.30, 0.22]**
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.59); I² = 0%								
Test for overall effect: Z = 0.30 (P = 0.76)								
2.1.2 Single session of moderate intensity aerobic exercise								
Boyne 2020	28.016	9.899	16	28.508	7.6	16	0.2%	-0.49 [-6.61, 5.62]
de Morais 2018	1.6853	0.2697	10	1.6405	0.3031	10	99.8%	0.04 [-0.21, 0.30]
Subtotal (95% CI)			26			26	100.0%	**0.04 [-0.21, 0.30]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 0.34 (P = 0.73)								
2.1.3 Single session of high intensity aerobic exercise								
Boyne 2020	30.957	8.837	16	26.196	9.643	16	4.7%	4.76 [-1.65, 11.17]
Boyne 2020	29.997	9.244	16	26.561	7.525	16	5.7%	3.44 [-2.40, 9.28]
Boyne 2020	26.929	7.68	16	25.335	9.331	16	5.5%	1.59 [-4.33, 7.52]
Charalambous 2018	15.51	5.07	12	17.16	6.31	12	9.2%	-1.65 [-6.23, 2.93]
Charalambous 2018	17.88	11.69	12	19.51	11.03	12	2.3%	-1.63 [-10.72, 7.46]
King 2019	48.36	26.7	35	45.3	25.5	35	1.3%	3.06 [-9.17, 15.29]
Mackay 2021	25.31	2.46	20	22.31	2.85	20	71.2%	3.00 [1.35, 4.65]
Subtotal (95% CI)			127			127	100.0%	**2.49 [1.10, 3.88]**
Heterogeneity: Chi² = 4.97, df = 6 (P = 0.55); I² = 0%								
Test for overall effect: Z = 3.51 (P = 0.0004)								
Test for subgroup differences: Chi² = 12.28, df = 2 (P = 0.002), I² = 83.7%								



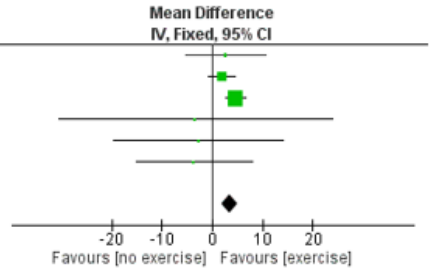
B

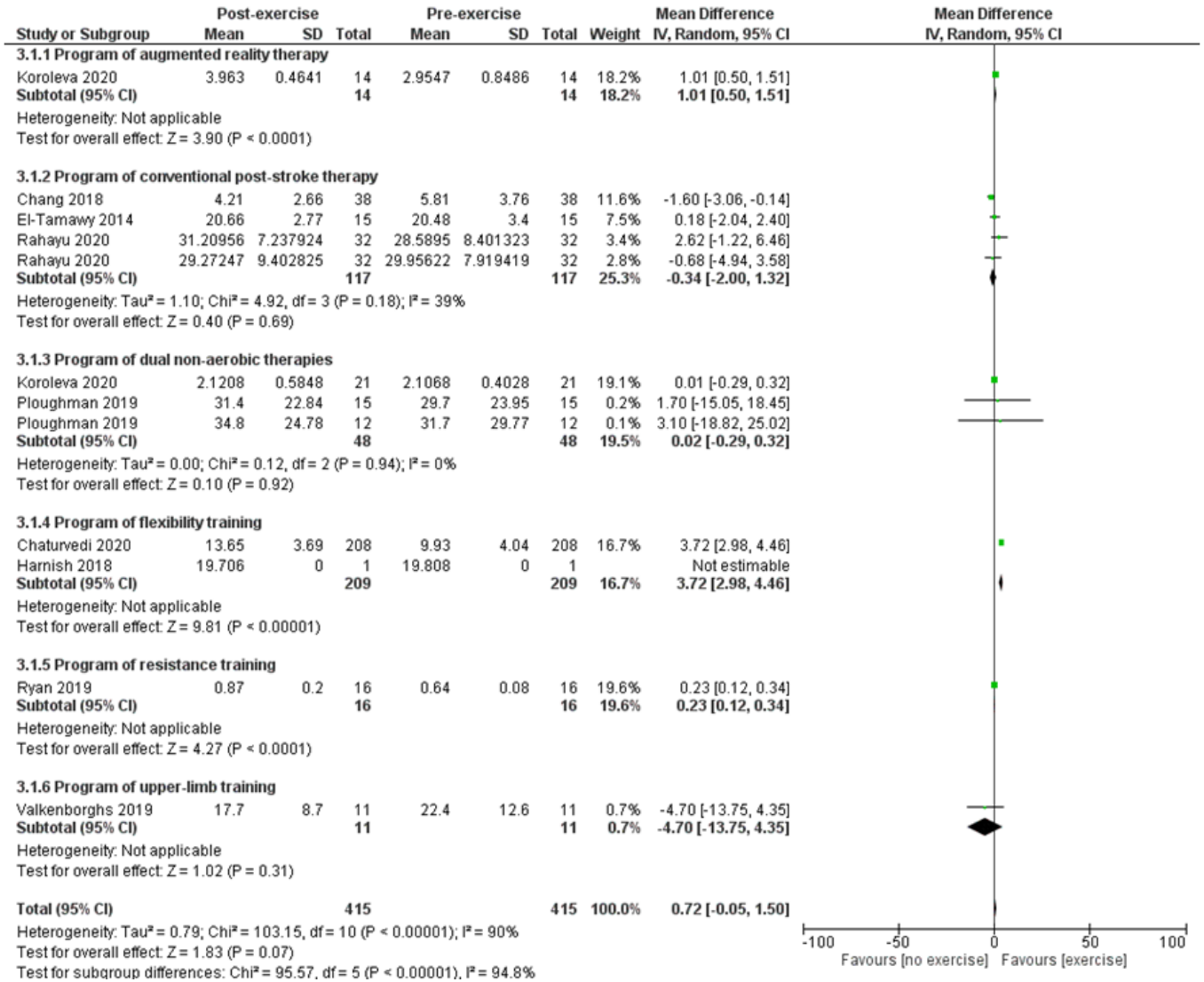
Study or Subgroup	Post-exercise Mean	SD	Total	Pre-exercise Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Harnish 2018	18.055	7.408	4	23.554	8.096	4	7.2%	-5.50 [-16.25, 5.26]
Hsu 2021	5.88	1.92	13	7.3	2.044	13	48.1%	-1.42 [-2.94, 0.10]
Kim 2019	21.455	2.196	9	19.528	2.021	9	44.7%	1.93 [-0.02, 3.88]
Total (95% CI)			26			26	100.0%	**-0.22 [-3.31, 2.88]**
Heterogeneity: Tau² = 4.57; Chi² = 7.96, df = 2 (P = 0.02); I² = 75%								
Test for overall effect: Z = 0.14 (P = 0.89)								



C

Study or Subgroup	Post-exercise Mean	SD	Total	Pre-exercise Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Harnish 2018	20.647	7.777	7	18.055	7.408	7	3.6%	2.59 [-5.36, 10.55]
Hsu 2021	7.91	2.866	10	6.06	3.159	10	32.3%	1.85 [-0.79, 4.49]
Kim 2019	23.596	2.067	9	18.992	2.088	9	61.3%	4.60 [2.68, 6.52]
Ploughman 2019	32.3	29.55	12	35.7	38.11	12	0.3%	-3.40 [-30.68, 23.88]
Ploughman 2019	26.5	19.11	13	29.3	24.5	13	0.8%	-2.80 [-19.69, 14.09]
Valkenborghs 2019	20.4	12.1	9	24.1	12.9	9	1.7%	-3.70 [-15.26, 7.86]
Total (95% CI)			60			60	100.0%	**3.42 [1.92, 4.92]**
Heterogeneity: Chi² = 5.08, df = 5 (P = 0.41); I² = 2%								
Test for overall effect: Z = 4.46 (P < 0.00001)								




Post-exercise
Pre-exercise
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
3.1.1 Program of augmented reality therapy
Koroleva 2020 3.963 0.4641 14 2.9547 0.8486 14 18.2% 1.01 [0.50, 1.51]
Subtotal (95% CI) 14 14 18.2% 1.01 [0.50, 1.51]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.90 (P < 0.0001)
3.1.2 Program of conventional post-stroke therapy
Chang 2018 4.21 2.66 38 5.81 3.76 38 11.6% -1.60 [-3.06, -0.14]
El-Tamawy 2014 20.66 2.77 15 20.48 3.4 15 7.5% 0.18 [-2.04, 2.40]
Rahayu 2020 31.20956 7.237924 32 28.5895 8.401323 32 3.4% 2.62 [-1.22, 6.46]
Rahayu 2020 29.27247 9.402825 32 29.95622 7.919419 32 2.8% -0.68 [-4.94, 3.58]
Subtotal (95% CI) 117 117 25.3% -0.34 [-2.00, 1.32]
Heterogeneity: Tau² = 1.10; Chi² = 4.92, df = 3 (P = 0.18); I² = 39%
Test for overall effect: Z = 0.40 (P = 0.69)
3.1.3 Program of dual non-aerobic therapies
Koroleva 2020 2.1208 0.5848 21 2.1068 0.4028 21 19.1% 0.01 [-0.29, 0.32]
Ploughman 2019 31.4 22.84 15 29.7 23.95 15 0.2% 1.70 [-15.05, 18.45]
Ploughman 2019 34.8 24.78 12 31.7 29.77 12 0.1% 3.10 [-18.82, 25.02]
Subtotal (95% CI) 48 48 19.5% 0.02 [-0.29, 0.32]
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
3.1.4 Program of flexibility training
Chaturvedi 2020 13.65 3.69 208 9.93 4.04 208 16.7% 3.72 [2.98, 4.46]
Harnish 2018 19.706 0 1 19.808 0 1 Not estimable
Subtotal (95% CI) 209 209 16.7% 3.72 [2.98, 4.46]
Heterogeneity: Not applicable
Test for overall effect: Z = 9.81 (P < 0.00001)
3.1.5 Program of resistance training
Ryan 2019 0.87 0.2 16 0.64 0.08 16 19.6% 0.23 [0.12, 0.34]
Subtotal (95% CI) 16 16 19.6% 0.23 [0.12, 0.34]
Heterogeneity: Not applicable
Test for overall effect: Z = 4.27 (P < 0.0001)
3.1.6 Program of upper-limb training
Valkenborghs 2019 17.7 8.7 11 22.4 12.6 11 0.7% -4.70 [-13.75, 4.35]
Subtotal (95% CI) 11 11 0.7% -4.70 [-13.75, 4.35]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)
Total (95% CI) 415 415 100.0% 0.72 [-0.05, 1.50]
Heterogeneity: Tau² = 0.79; Chi² = 103.15, df = 10 (P < 0.00001); I² = 90%
Test for overall effect: Z = 1.83 (P = 0.07)
Test for subgroup differences: Chi² = 95.57, df = 5 (P < 0.00001), I² = 94.8%
-100 -50 0 50 100
Favours [no exercise] Favours [exercise]