Post-Stroke Depression:
Trajectory and Association with Patient Perceived Recovery

Submitted by

Katherine Sewell

BOccThy, BPsySc, MPH

A thesis submitted in total fulfilment of the requirements for the degree of Doctor of Philosophy.

Department of Occupational Therapy, Social Work and Social Policy
School of Allied Health, Human Services and Sport
College of Science, Health and Engineering
La Trobe University
Victoria, Australia

August 2021

Table of Contents:

Preliminary Material

Table of Contents:

Thesis Chapters

Statement of Authorship

This thesis includes work by the candidate that has been published, accepted or under consideration for publication, as described in the text. Expect where reference is made in the text of the thesis, this thesis contains no material published elsewhere or extracted in whole, or in part, from a thesis submitted for the award of any other degree or diploma. No other person's work has been used without due acknowledgement in the main text of the thesis. The studies presented in this thesis that have been published, accepted or under consideration for publication involve joint authorship. This thesis has not been submitted for the award of any degree or diploma, in any other tertiary institution. This research was supported by a La Trobe University Postgraduate Research Scholarship.

Katherine Sewell

28 August 2021

Acknowledgements

Acknowledgement of Country

I am privileged to live, work and learn on the ancestral and unceded lands of the Boon Wurrung people of the Kulin nation. I acknowledge Aboriginal and Torres Strait Island peoples, past and present, as the traditional owners and continuing custodians of the land. I pay respect to Elders of the community and extended my recognition to their descendants.

General Acknowledgements

Thank you to my supervisors Leeanne Carey and Tamara Tse. Thank you for your willingness to share your knowledge and skills, for your valuable time which you have invested me, and for your encouragement to celebrate even the smallest of triumphs – and importantly, your support and motivation during the more challenging moments.

Thank you to my colleagues and my co-authors who have shared their time, expertise and experiences. This work would not have been possible without your support and valuable contributions. I also wish to express my gratitude to the stroke survivors and their families who generously gave their time to this research.

Thank you to my ever supportive partner Tom, who at times, I am sure, felt replaced by my laptop or a journal article. Thank you for ensuring a coffee was always the start of my day. Thank you for always cooking me dinner – even on the countless occasions I continued to work for "just a bit longer", when I had told you I would help with dinner. Your endless understanding, patience and support has been, and will always be, truly appreciated.

A heartfelt thank you to my generous, humble and hardworking sister, Julia. I am very lucky to have had your support and encouragement of my progress with my thesis, as well as with many other endeavours. Thank you for all the advice you have given me, and for providing a voice of reason during periods of uncertainty. My life is continuously enriched by your generosity, wisdom and love. To Scott, thank you for your continuing curiosity in my research. I am delighted to share so many interests with you, and I'm excited to see the academic accomplishments that you will achieve.

To my compassionate and intelligent friends, I thank you for celebrating each of my accomplishments and for maintaining my interests beyond my PhD. Each of you inspire and motivate me to be a better person. I am lucky to be surrounded by such strong and beautiful women.

Dedication

I dedicate this thesis to my Mum and Dad:
Marie and Michael Sewell.

I am profoundly aware of my privilege to have received many years of education. This is due, largely, to you both.

Thank you for instilling in me the values of education and health, and for teaching me that I am fortunate to receive an education and to be in good health. Thank you for showing me that success is determined by hard work, courage, and most importantly, compassion. Thank you for teaching me there is always time for a coffee.

Mum and Dad, your immeasurable love and support has sustained me through this journey.

At times, when I felt hopeless and concerned about the purpose and significance of my work, my Mum and Dad reminded me of its value.

"Your thesis is like a brick in a wall, in a house, in a town, in the world. On its own, it may not feel like it provides a significant contribution, but it has an important place and supports the other bricks in the wall, in the house, in the town, in the world"
– Michael Sewell

Format, Structure and Style

Format and Structure of this Thesis

This thesis comprises 10 chapters, four of which contain articles that have been published, accepted or submitted for publication; these articles are presented in Chapters 5, 6, 7 and 8.

Articles which have been published, accepted or submitted for publication have been formatted consistently in the style of this thesis, independent of the style required by the journal to which each manuscript was submitted.

Tables and figures for each study are presented in the body of the manuscript. Supplementary material for the empirical research studies (Chapters 5, 7 and 8) are presented at the end of each study, within the relevant chapter. Additional materials for all other chapters are presented in the appendices, at the end of this thesis. All in-text citations are organised in a single reference list at the end of the thesis.

Style of this Thesis

This thesis has been written in Australian English and the style is based on guidelines published by the American Psychological Association (APA) seventh edition (American Psychological Association, 2019). This guide provides suggestions and examples of effective and scholarly communication, which I have adopted in this thesis. However, some minor deviations from the APA style guide and some additional style decisions are used throughout this thesis. This style, based on APA, reflects my voice and personal writing style. All writing, grammar, and style decisions have been uniformly applied throughout this thesis.

A Preliminary Note on Terms Used in this Thesis

Cohort (*N*) and sample (*n*)

When the term 'cohort' (*N*) is used, this is in reference to the total START cohort which comprises 219 stroke survivors, with the exception of the use of this term in the Review (Chapter 2), when reference is made to individual cohorts of the included studies. When the term 'sample' (*n*) is used, this refers to the samples from the total START cohort and analysed in the empirical research studies (Chapters 5, 7 and 8).

Depression and depressive symptoms

The terms 'depression' and 'depressive symptoms' are used in the context of post-stroke depression. In the empirical research studies (Chapters 5, 7 and 8), the term 'depressive symptoms' is operationally defined as scores on the Montgomery-Åsberg Depression Rating Scale (MADRS). The presence of depressive symptoms is defined by a score above a threshold on a validated measure for depressive symptoms. The diagnosis of 'depression' is defined by the clinical diagnosis of minor or major depression according to the Diagnostic Statistical Manual (DSM). The presence of depressive symptoms detected by a validated questionnaire is considered an acceptable surrogate marker for depression in this body of research; however, the terms are not used interchangeably.

Screening measures

The terms 'screening measure', 'screening tool', and 'screening instrument' are used synonymously throughout this thesis.

Patients, participants and stroke survivors

The terms 'patient', 'participant', and 'stroke survivor' are used to refer to the individuals enrolled in the START research program – and more generally, to describe individuals who have had a stroke. For the most part, these terms are used interchangeably throughout this thesis. The term 'patient' is used to describe an individual during the acute phase after stroke and relative to their status as a patient receiving medical care or treatment in a hospital setting. The term 'participant' is adopted in the context of the study design and research program. The term 'stroke survivor' is employed when it is no longer accurate to define the individual by a patient role, such as following discharge from the hospital setting to their home – and in the context of their recovery and long term outcomes. The preferred term used in this context is 'stroke survivor', and where suitable, it is used to acknowledge and promote an individual's active involvement in clinical decision making and to avoid defining an individual only by their illness.

Nonstandard Abbreviations and Acronyms

ADL	Activities of Daily Living
AFFINITY	Assessment of Fluoxetine in Stroke Recovery (a randomised controlled trial)
AIDS	Acquired Immune Deficiency Syndrome
APA	American Psychiatric Association (DSM)
APA	American Psychological Association (style guide)
AuSCR	Australian Stroke Clinical Registry
BDI	Beck Depression Inventory
BI	Barthel Index
CCI	Charlson Comorbidity Index
CDS	Cornell Depression Scale
CES-D	Center for Epidemiological Studies – Depression
CIDI	Composite International Diagnostic Interview
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIS-R	Clinical Interview Schedule – Revised
DALY	Disability-Adjusted Life Year
DSM	Diagnostic and Statistical Manual of Mental Disorders
eCRF	Electronic Case Report Form
EFFECTS	Efficacy of Fluoxetine – a Randomised Controlled Trial in Stroke
EXTEND	Extending the Time for Thrombolysis in Emergency Neurological Deficits
FAST	Face, Arms, Speech, Time (a public health campaign)
FOCUS	Fluoxetine Or Control Under Supervision (a randomised controlled trial)
GBD	Global Burden of Disease (The Global Burden of Disease Studies)
GDS	Geriatric Depression Scale
GP	General Practitioner or General Practice
HADS-D	Hospital Anxiety and Depression Scale – Depression subscale
HDRS	Hamilton Depression Rating Scale
ICD	International Classification of Disease
MADRS	Montgomery-Åsberg Depression Rating Scale
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NTA	National Trials Australia
PHQ	Patient Health Questionnaire
PrePARE	Prediction and Prevention to Achieve Optimal Recovery Endpoints after Stroke
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews

RDI	Rome Depression Inventory
SIGMA	Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale
SRRR	Stroke Recovery and Rehabilitation Roundtable
SSRI	Selective Serotonin Reuptake Inhibitors
START	Stroke Imaging Prevention and Treatment collaborative research program
tPA	Tissue Plasminogen Activator
VAS	Visual Analogue Scale
WHO	World Health Organisation
WSAS	Work and Social Adjustment Scale
ZSRD	Zung Self-Rating Depression

Statistical Notation

α	significance level (alpha)
CI	condition index
CI	confidence interval (95% CI)
CN	condition number
IQR	interquartile range (Q1, Q3)
M	mean
Mdn	median
N	cohort
n	sample
OR	odds ratio
p	*p* value
Q1	quantile 1, 25^{th} percentile
Q2	quantile 2, 50^{th} percentile, median
Q3	quantile 3, 75^{th} percentile
SD	standard deviation
SE	standard error
VIF	variance inflation factor
z	z-value (for the 0.95 probability)

Thesis Abstract

Approximately one-third of stroke survivors experience depression, when assessed at any time after stroke. However, post-stroke depression appears to vary in timing of onset, course, and duration. A major aim of this thesis was to characterise the trajectory of post-stroke depression in a longitudinal cohort. Further, as depression is known to impact recovery post-stroke, the association between post-stroke depression and a profile of recovery outcomes was investigated.

The first empirical study (Chapter 5) found that half of stroke survivors in a longitudinal national stroke cohort ($N = 219$) varied in their status of depressive symptoms during the first year. Further, stroke survivors with depressive symptoms at 3 months were more likely to have depressive symptoms at 12 months, compared to those without such symptoms at 3 months. The dynamic trajectory identified questions about the most effective timing of screening for post-stroke depression. Current Australian guidelines state there is insufficient evidence to determine optimal timing – but suggest that stroke survivors with suspected altered mood be assessed. The perspective article (Chapter 6) presented evidence for the optimal timing and frequency of screening. An update is recommended that promotes routine and repeated screening of all stroke survivors – not just those with suspected altered mood.

The second empirical study (Chapter 7) demonstrated significant associations between depressive symptoms and recovery during the first year post-stroke – when measured by four patient-reported outcome measures, but not by an observer-rated measure. Patient-reported outcome measures may better reflect the impact of depressive symptoms post-stroke.

The third empirical study (Chapter 8) demonstrated significant associations between pre-existing comorbidity burden and patient perceived impact post-stroke. The use of patient-reported outcome measures, alongside observer-rated measures, provides a more complete picture of overall recovery.

Collectively, these findings advance the current literature pertaining to post-stroke depression, its trajectory, and its association with patient perceived recovery.

Thesis Outline

Chapter 1. General Introduction

The first chapter is an overall introduction to this thesis in which the three key concepts, 'stroke', 'post-stroke depression' and 'recovery', are defined and described. The primary aims and research questions are outlined.

Chapter 2. Review: Trajectory of Depressive Symptoms Following Stroke

The second chapter presents a comprehensive review of longitudinal cohort studies that evaluate depression or depressive symptoms following stroke, at two or more time points. This review identifies and characterises all relevant studies, to better understand the trajectory of post-stroke depression.

Chapter 3. Common Methodology

The third chapter provides a detailed description of the common methodology used in the three empirical research studies in this thesis. This chapter introduces the Stroke Imaging Prevention and Treatment (START) collaborative research program, which provides the data for the empirical research. This is followed by a description of the measures and statistical methods which are utilised in the empirical research studies.

Chapter 4. START Cohort Characteristics

The fourth chapter presents the design and cohort characteristics of the START research program, from which each empirical research study utilises samples of participants. The chapter also compares demographic and clinical characteristics of the START cohort with those of the Australian Stroke Clinical Registry (AuSCR).

Chapter 5. Empirical Study 1: Trajectories and Associations of Depressive Symptoms

The fifth chapter presents the first empirical research study of this thesis. This study describes changes and associations in the course of depressive symptoms over the first year post-stroke. The status of depressive symptoms, experienced by stroke survivors in a sample from the START cohort, is evaluated at three time points: within the first week, at 3 months and at 12 months post-stroke.

Chapter 6. Perspective: Screening for Post-Stroke Depression

The sixth chapter presents a Perspective Article. This article explores current Australian practice regarding screening for post-stroke depression. It presents evidence for the optimal timing and frequency of screening and recommends an update to current national guidelines.

Chapter 7. Empirical Study 2: Depressive Symptoms and Recovery Outcomes

The seventh chapter presents the second empirical research study of this thesis. This study explores associations between post-stroke depressive symptoms and recovery, as measured across a profile of commonly used outcome measures. Samples of stroke survivors from the START cohort are utilised for each of the analyses, at 3 months and 12 months following stroke.

Chapter 8. Empirical Study 3: Comorbidity Burden and Perceived Recovery

The eighth chapter presents the third empirical research study of this thesis. This study explores the associations between pre-existing comorbidity burden and patient perceived recovery outcomes following stroke. Samples of stroke survivors from the START cohort are utilised for each of the analyses, at 3 months and 12 months post-stroke.

Chapter 9. General Discussion

The penultimate chapter discusses the main findings and key themes that have emerged from the research presented in this thesis, in the context of existing literature and current clinical practice. This chapter also presents implications for clinical practice and recommendations for future research. It continues with a brief discussion of limitations to the research in this thesis, and of related concepts.

Chapter 10. Overall Conclusion

The final chapter presents the conclusions pertaining to the research findings of this thesis. It reflects on the primary aims and research questions, summarises the findings of this research and highlights their collective importance. This concluding chapter demonstrates how this thesis advances the current literature and provides an opportunity to improve clinical practice in the management of post-stroke depression.

Contribution of Others to Work Presented in this Thesis

I would like to acknowledge the contributions of others to the work presented in this thesis.

Professor Leeanne M. Carey (principal supervisor) and Dr Tamara Tse supervised the research presented in this thesis. They provided substantial input, from the inception of each study until completion. Both supervisors contributed to the conceptualisation and design of the three empirical research studies, the perspective article and the review. Further, they provided feedback and reviewed final versions of the written material included in this thesis. Professor Carey conceptualised and was principal investigator for the longitudinal stroke cohort study of the START program of research.

Adjunct Professor Thomas A. Matyas chaired the progress panel for the research program. He provided advice regarding the statistical methods and interpretation of results of the third empirical research study.

Professor Leonid Churilov provided expert advice pertaining to the study design, statistical methods and interpretation of results of the three empirical research studies. He reviewed the final version of each empirical research study.

Professor Geoffrey A. Donnan provided expert opinion and feedback regarding the three empirical research studies and the perspective article.

Professor Henry Ma and Professor Stephen M. Davis provided feedback regarding the written work and interpretations of results of the three empirical research studies.

Dr Elizabeth Harris assisted with the statistical methods and interpretation of results of the third empirical research study. She reviewed iterations of the manuscript, including the final version.

Professor Thomas Lindén and Professor Shelia Crewther provided feedback regarding the second empirical research study.

Dr Julia Sewell and Dr Juan Pablo Saa contributed to the review.

Importantly, I would like to acknowledge that Professor Leeanne M. Carey, Professor Geoffrey A. Donnan, Professor Leonid Churilov, Professor Henry Ma, Professor Stephen M. Davis, Professor Thomas Lindén and Professor Shelia Crewther were all named investigators involved in the establishment of the START collaborative research program, which includes both START PrePARE and START EXTEND arms.

Publications, Presentations and Awards Related to this Thesis

Publications related to this thesis

Sewell, K., Tse, T., Donnan, G. A., & Carey, L. M. (2021). Screening for Post-Stroke Depression: Who, When and How? *Medical Journal of Australia*; in press © Copyright 2021. *The Medical Journal of Australia*. Reproduced with permission.

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

Sewell, K., Tse, T., Churilov, L., Ma, H., Davis, S. M., Donnan, G.A., & Carey, L. M. (2021). Trajectories and Associations of Depressive Symptoms at Acute, Subacute and Chronic Phases in a Longitudinal Stroke Cohort. [Manuscript submitted for publication].

Sewell, K., Tse, T., Churilov, L., Lindén, T., Crewther, S., Ma, H., Davis, S. M., Donnan, G. A., & Carey, L. M. Depressive Symptoms are Associated with Patient Perceived Recovery Outcomes at 3 and 12 months Post-Stroke. [Manuscript submitted for publication].

Conference presentations related to this thesis

Screening for Post-Stroke Depression – Who, When and How? What Australia Can Learn from International Guidelines. Oral presentation. Organisation for Psychological Research into Stroke (OPSYRIS) conference. Online, December 2021.

Depressive Symptoms are Associated with Patient Perceived Recovery Outcomes at 3 and 12 months Post-Stroke. Oral presentation. Organisation for Psychological Research into Stroke (OPSYRIS) conference. Online, December 2021.

Depressive Symptoms are Associated with Patient Perceived Recovery Outcomes at 3 and 12 months Post-Stroke. Poster presentation. School of Allied Health, Human Services, and Sport Graduate Student Conference, La Trobe University. Melbourne, Australia, December 2021.

Trajectory of Depressive Symptoms After Stroke: A Longitudinal Australian Cohort Study. Poster presentation. 11th World Congress for Neurorehabilitation (WFNR) and the 35th Congress of the French Society of Physical and Rehabilitation Medicine. Online, October 2020.

Exploring the Trajectory of Depressive Symptoms Post-Stroke in an Australian Cohort. Oral presentation. Stroke Society of Australasia (SSA) conference. Canberra, Australia, September 2019.

Depressive symptoms post-stroke are independently associated with perceived recovery outcomes within the first year. Poster presentation. Stroke Society of Australasia (SSA) conference. Canberra, Australia, September 2019.

Depressive symptoms post-stroke are independently associated with poorer perceived recovery outcomes. Oral presentation. Victorian Allied Health Research Conference. Melbourne, Australia, March 2019.

Pre-existing comorbidities are independently associated with recovery outcomes. Stroke Society of Australasia (SSA) conference. Poster and oral presentation. Sydney, Australia, August 2018.

Awards related to this thesis

First place award for poster presentation: Depressive Symptoms Are Associated with Patient Perceived Recovery Outcomes at 3 and 12 months Post-Stroke. School of Allied Health, Human Services, and Sport Graduate Student Conference, La Trobe University. Melbourne, Australia, December 2021.

First place award for oral and poster presentation: Pre-existing comorbidities are independently associated with recovery outcomes. Stroke Society of Australia (SSA) conference. Sydney, Australia, August 2018.

Lists of Tables, Figures and Appendices

List of Tables

Chapter 8. Empirical Study 3: Comorbidity Burden and Perceived Recovery

List of Figures

Chapter 2. Review: Trajectory of Depressive Symptoms Post-Stroke

Chapter 3. Common Methodology

Chapter 5. Empirical Study 1: Trajectories and Associations of Depressive Symptoms

Chapter 9. General Discussion

List of Appendices

Prologue

Mental health and illness interacts with physical health and illness to affect health outcomes. However, in clinical practice and research, mental illness and physical illness are often managed in silos, independent of each other. The intersection of mental health and physical health is complex. The collaborative and holistic management of both health states requires creative thinking, multiple perspectives, and importantly, the perspective of the patients who are personally impacted.

Chapter 1.

General Introduction

"You ought not to attempt to cure …
the body without the soul … for the
part can never be well unless the whole is well."

Plato, *Charmides*
(Lipowski, 1985, p. 105)

There are three key concepts that underpin the research presented in this thesis: stroke, post-stroke depression, and recovery. Each of the key concepts, and the thesis aims and research questions, are described in the subsequent sections, as follows:

- 1.1 Stroke
- 1.2 Post-Stroke Depression
- 1.3 Recovery
- 1.4 Thesis Aims and Research Questions

1.1 Stroke

1.1.1 Definition and classification

In the mid-twentieth century, the term 'apoplexy', first introduced by Hippocrates, the founder of medicine, was formally replaced in the modern medical lexicon by the term 'stroke' (Coupland et al., 2017; Engelhardt, 2017). A modern definition of stroke, published by the World Health Organisation (WHO) in 1971, was "the sudden onset of a focal neurological deficit due to a local disturbance in blood supply to the brain" (World Health Organisation, 1971, p. 6). In 1980, the WHO refined this to the current, widely accepted definition of "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" (Aho, 1980, p. 114).

Stroke is classified as a cerebrovascular disease; a stroke occurs when an artery in the brain is either occluded or ruptures, causing disruption to the brain's blood supply (Sacco, 2013). Subtypes of stroke include ischaemic stroke (also known as cerebral infarction) due to arterial occlusion, and haemorrhagic stroke (including intracerebral haemorrhage and subarachnoid haemorrhage) due to arterial rupture (Aho, 1980; Campbell et al., 2019). Approximately 70 to 85 per cent of strokes are ischaemic (Robinson & Jorge, 2016; Phipps & Cronin, 2020).

1.1.2 The global burden

Globally, stroke is a major health issue and is a leading cause of death and disability (Cheung, 2014; Katan & Luft, 2018). The most recent Global Burden of Disease (GBD) Study estimates the annual incidence of stroke to be greater than 13 million worldwide (Johnson et al., 2019). The GBD Study estimates there were 5.5 million deaths due to stroke in 2016 (Johnson et al., 2019); this equates to more than 10 per cent of deaths from all causes worldwide (Feigin et al., 2018). There were more than 80 million survivors of stroke in 2016; it is estimated that more than 116 million disability-adjusted life years (DALYs) are lost each year, due to stroke-related death and disability (Johnson et al., 2019). Further, the estimated global lifetime risk of stroke, for those aged 25 years and older, is 25 per cent (Feigin et al., 2018). Globally, the burden of stroke has increased substantially over the past few decades due to an acceleration in population growth and an aging population (Katan & Luft, 2018). The number of stroke survivors who will require ongoing care by clinicians, their families and their communities will continue to grow in coming decades (Katan & Luft, 2018).

1.1.3 The national burden

In Australia, stroke is similarly recognised as a major health problem. In 2020, there were an estimated 27,000 cases of first ever stroke (Deloitte Access Economics, [DAE] 2020a) and approximately 8,000 deaths (DAE, 2020). Approximately half a million Australians are living with stroke (Deloitte Access Economics [DAE], 2020b). This number is expected to increase to 700,000 within the next decade (DAE, 2020b). The DALYs lost due to stroke was estimated to be more than 120,000 years in 2020 (DAE, 2020b). In developed countries, such as Australia, acute medical interventions for stroke have advanced substantially, with treatments such as thrombolysis and endovascular clot retrieval (Wardlaw et al., 2014; Campbell 2016). In metropolitan areas, initiatives such as the Mobile Stroke Unit facilitate early treatment of stroke (Zhao et al., 2021). In addition, public awareness of the signs of stroke have increased, largely attributed to public health campaigns such as the mnemonic device using the acronym 'FAST' (Face, Arm, Speech, Time) (Wolters et al., 2018). These advances are resulting in less brain cell death and improved survival following stroke (Campbell et al., 2019). Despite these advances, Australian Aboriginal and Torres Strait Islanders have a higher incidence of stroke than non-

Indigenous Australians (Katzenellenbogen et al., 2011), and evidence has demonstrated poorer quality of care and recovery outcomes (Kilkenny et al., 2013; Tiedman et al., 2019).

1.1.4 The individual burden

A stroke survivor may experience any, some, or all of the wide range of deficits caused by stroke. Stroke-related deficits can be categorised according to the neuropsychological system impacted, listed as follows:

- motor deficits, including: hemiplegia (paralysis of one side of the body); hemiparesis (weakness of one side of the body); monoplegia (paralysis of one limb); monoparesis (weakness of one limb); and ataxia (impaired coordination)
- somatosensory deficits, including: hemihypoaesthesia (reduction of sensation, such as touch or proprioception, on one side of the body); paraesthesia (abnormal sensation, such as 'pins and needles'); and neuropathic pain
- visual deficits, including hemianopia (loss of vision in half of the visual field)
- autonomic deficits, including incontinence (loss of bladder or bowel control)
- communication deficits, including: expressive aphasia (inability to speak); receptive aphasia (inability to understand speech); expressive dysphasia (difficulty speaking); and receptive dysphasia (difficulty understanding speech)
- cognitive deficits, including: amnesia (impaired memory); anosognosia (inability to acknowledge the full extent of impairments resulting from stroke); neglect (the loss of ability to respond to objects or stimuli); and apraxia (the loss of ability to carry out a planned, purposeful sequence of movements)
- psychological deficits, including: grief, anxiety, emotional lability, fatigue – and importantly, post-stroke depression

As a result of these deficits, stroke survivors may experience profound and often long-term limitations in their everyday lives. For example, stroke survivors may experience limitations in mobility (such as walking, transferring and using stairs), in activities of daily living (such as cooking, cleaning, shopping and using public transport), in activities of self-care (such as bathing, dressing and toileting), in social participation (such as conversing and communal dining) and in returning to previous occupations and roles (such as employment, volunteerism, parenting and caregiving). The impact of stroke-related deficits can vary significantly; as a result, stroke survivors can experience 'minimal' to 'full' recovery. Many stroke survivors experience recovery to some degree; however, two-thirds live with impairments which affect their overall quality of life (DAE, 2020a; DAE, 2020b).

1.2 Post-Stroke Depression

1.2.1 Definition and classification

Post-stroke depression has been recognised in medical literature over the last 100 years; in 1924, 'chronic melancholia' was described following stroke (Gaete & Bogousslavsky, 2008; Robinson & Jorge, 2016). The earliest empirical research of post-stroke depression was conducted in the mid-twentieth century. In 1955, Roth demonstrated an association between atherosclerotic disease and depression (Roth, 1955). In 1977, Folstein and colleagues suggested that post-stroke depression was not solely a psychological response, because of the observed higher prevalence of depression among stroke patients when compared to a cohort of orthopaedic patients with comparable functional disabilities (Folstein et al., 1997).

At the present time, post-stroke depression is a well-documented sequela of stroke (Das & Rajanikant, 2008). Post-stroke depression is classified in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) within the category 'Mood disorders due to another medical condition'. The DSM-5 defines post-stroke depression as "a prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities that predominates in the clinical picture and that is thought to be related to the direct physiological effects of another condition [stroke]" (American Psychiatric Association [APA], 2013a). Using the DSM-5 criteria, the diagnosis of post-stroke depression requires a comprehensive psychiatric interview to determine the presence of at least five depressive symptoms, with at least one being either depressed mood (feelings of sadness) or anhedonia (loss of interest or pleasure) (APA, 2013a). Other symptoms include feelings of worthlessness or guilt, thoughts of death or suicide, changes in sleep, changes in motor activity, changes in appetite and weight, and difficulty in concentrating and thinking. To reach diagnostic criteria, these symptoms need to be persistent – that is, experienced almost every day for at least two weeks (APA, 2013a). Further, numerous measures of depressive symptoms are available to screen for depression in clinical practice (Guo et al., 2021).

1.2.2 Aetiology and pathophysiology

The aetiology and pathophysiology of post-stroke depression are complex and are not completely understood (Gaete & Bogousslavsky, 2008; Khan, 2008; Das & Rajanikant, 2018). They are likely to be multifactorial, with interacting biological and psychosocial components (Towfighi et al., 2017; Terril et al., 2018). Biological factors that have been proposed as contributors to the onset and development of post-stroke depression include: genetic susceptibility; demographic factors including age and sex; stroke type and lesion location; inflammatory response in the brain following stroke; alterations in serotonergic, noradrenergic and dopaminergic neurotransmission pathways; and neurogenesis and neuroplasticity in response to ischemia (Gaete & Bogousslavsky,

2008; Fang & Cheng, 2009; Pascoe et al., 2011; Robinson & Jorge, 2016; Das & Rajanikant, 2018; Terril et al., 2018).

Psychosocial factors that have been proposed as contributors to the onset and development of post-stroke depression include: personal psychiatric history including pre-stroke depression; family psychiatric history; limitations of support and resources; impact of loss of independence; impact of cognitive deficits; and impact of communication impairment (Dafer et al. 2008; Das & Rajanikant, 2018). However, further research is needed to advance our understanding of the aetiology and pathophysiology of post-stroke depression (Towfighi et al., 2017).

1.2.3 Prevalence and trajectory

Depression is a common sequela of stroke. Two highly cited epidemiological studies used meta-analysis to aggregate data from numerous observational studies to determine the prevalence of post-stroke depression. Hackett and Pickles (2014) reported that 31 per cent of stroke survivors were classified as experiencing depression, at any time, within the first five years (95% CI [28, 35]). Ayerbe et al. (2013) found a 29 per cent prevalence of post-stroke depression, at any time, during the first 10 years (95% CI [25, 32]).

Depression is more prevalent in stroke survivors compared with the general adult population, which is reported to be approximately 13 per cent (Lindén et al., 2007; Lim et al., 2018). Further, post-stroke depression is also more common than the 17 per cent prevalence observed in cancer survivors (Mitchell et al., 2011; Götze et al., 2019) and the 15 to 20 per cent prevalence reported in myocardial infarction patients (Thombs et al., 2006; Shapiro, 2015).

The prevalence of post-stroke depression reported across observational cohort studies varies. This is probably due, largely, to differences in the demographic and clinical characteristics of the cohorts studied (age, sex, stroke severity, premorbid depression, previous stroke, communication or cognitive impairments) and in the settings where the studies were conducted (acute stroke units, general hospital wards, rehabilitation centres or community settings). In addition, differences are partially due to the variety of assessment methods used (diagnostic interview or screening measure with a cut-off score) and the time elapsed since stroke (acute, subacute, chronic) (Gaete & Bogousslavsky, 2008). Despite these methodological variations, it is generally recognised that approximately 30 percent of stroke survivors experience depression, or depressive symptoms, at any time after stroke (Guo et al., 2021).

Among individual stroke survivors, post-stroke depression has a dynamic trajectory (Ayerbe, 2013b). The term ‘trajectory’, in the context of post-stroke depression, encompasses the following temporal characteristics: the latency of onset, the course, and the duration. Regarding the latency

of onset, most episodes of depression start within the first year, with one-third identified during the first three months (Ayerbe, 2013b). However, for the remaining two-thirds, depression does not develop until after three months and may not emerge for many months, or even years, after stroke (Ayerbe, 2013b). The course of post-stroke depression may be episodic or persistent (Mitchell, 2016). The duration of post-stroke depression can refer either to the duration of individual episodes in a recurring course, or to the total duration of post-stroke depression until complete resolution. Ayerbe et al., (2013a) highlighted the need for long term studies to investigate the prevalence of depression at different time points, the timing of depression onset and recovery, and recurrence patterns. Further longitudinal research exploring the trajectory of post-stroke depression will improve our understanding of the condition and will provide insight into its detection and management.

1.2.4 Assessment of depression and depressive symptoms

The terms 'depression' and 'depressive symptoms' are often used synonymously in health literature; however, it is important to distinguish these, because the two terms are not exactly equivalent. Depression is a clinical diagnosis that requires a comprehensive psychiatric interview, conducted by a trained practitioner to assess for the presence of specific criteria outlined in the DSM (Mitchell, 2016). In contrast, depressive symptoms indicate the possible presence of depression – but on their own are not diagnostic of depression. The presence and severity of depressive symptoms can be evaluated using a questionnaire that has been designed specifically for this purpose. Such questionnaires can be used as screening measures when validated cut-off scores are employed; cut-off scores vary and can be set to a preferred specificity and sensitivity. In the context of post-stroke depression, the purpose of a screening measure is to detect stroke survivors with the possible presence of depression, following which a diagnosis can be confirmed or refuted by psychiatric interview (Mitchell, 2016).

The assessment of depression, or depressive symptoms, following stroke can be particularly difficult due to several factors. The presence of post-stroke cognitive and communication impairments, such as aphasia, agnosia, apraxia, memory deficit, and anosognosia may make it challenging for stroke survivors to accurately respond to questionnaires and interviews (Khan, 2004; Gaete & Bogousslavsky, 2008). In addition, the overlap of somatic symptoms, which may be due either to stroke or to depression (such as fatigue, reduced concentration, insomnia and reduced appetite), makes it more difficult to distinguish the origin of such symptoms (de Coster et al. 2005). Further, the presence of psychological symptoms in response to an acute adverse health event (such as grief, uncertainty, denial, despair, and emotional lability) can also affect the assessment for depression or depressive symptoms, particularly in the acute phase (Hermann & Wallesch, 1993; Dafer et al. 2008).

1.3 Recovery

1.3.1 Terminology

Following stroke, the term 'recovery' is usually considered to indicate 'overall recovery' when used without the addition of any qualification. When evaluating any one specific facet of recovery after stroke, the term recovery should be qualified by the name of the particular system or function that is being assessed, for example 'motor recovery' or 'functional recovery'. Overall recovery following stroke is multidimensional because stroke causes a greater range of residual deficits than many other medical conditions (Dowswell et al., 2000; Adamson et al., 2004). These include deficits in motor, sensory, autonomic systems, and deficits in communication, cognitive and psychological functions. Overall recovery after stroke is complex because of the unique circumstances and contextual factors experienced by each individual stroke survivor. Further, the impact of stroke on an individual's recovery changes over time (Mayo et al., 1999).

The importance of considering overall recovery in the context of an individual's life after stroke has been highlighted by qualitative interviews which have demonstrated that stroke survivors "do not usually perceive the various aspects of their lives – physical, emotional and social – as separate or fragmented" (Dowswell et al., 2000, p. 510). Further, overall recovery should be considered in the context of an individual's life prior to stroke. Qualitative interviews have also shown that stroke survivors utilise personal benchmarks and expectations for recovery, relative to their life before the stroke (Gubrium et al., 2008).

In stroke literature, there does not appear to be a widely accepted, conceptual definition of 'overall recovery'. When definitions of recovery have been proposed, these appear to focus solely on functional recovery and motor recovery (Levin et al., 2009; Bernhardt et al., 2017). The Stroke Recovery and Rehabilitation Roundtable (SRRR) acknowledged, regarding recovery outcomes, that "the motor system has been studied more than any other [system] in stroke research" (Bernhardt et al., 2017, p. 445). This is probably because functional and motor impairments have conventionally been regarded as the hallmarks of stroke-related deficits; accordingly, the primary focus of rehabilitation has been to improve physical function and independence (Vanhook, 2009).

The term 'recovery' has seldom incorporated psychological, social and contextual factors, including the resources and supports available to the stroke survivor, which are also known to impact recovery (Horgan et al., 2009). The preponderant use of functional and motor recovery outcome measures may be misleading in terms of what constitutes a 'successful' recovery (Jones et al., 2008). In stroke research and practice, there is a need to develop the definition and measurement of overall recovery, to encompass not only physical but also non-physical factors (Vanhook, 2009).

1.3.2 Post-stroke depression and recovery

Stroke survivors with depression do not recover as well as those without depression. There is a considerable body of research that demonstrates the effects of depression on recovery following stroke. Stroke survivors with depressive symptoms have longer lengths of hospital stay compared with non-depressed stroke patients (Sugawara et al., 2015). The presence of depressive symptoms hinders stroke patients' ability and motivation to participate in rehabilitation (Hermann & Wallesch, 1993; Gillen et al., 2001; Kapoor et al., 2019). Following the acute phase, stroke survivors with depression experience poorer functional recovery (Matsuzaki et al., 2015) and have greater residual disability (Ayerbe et al., 2013a; Kutlubaev & Hackett, 2014) compared to those without post-stroke depression. Similarly, stroke survivors with depression experience greater dependence in undertaking activities of daily living (ADL) (Amaricai & Poenaru, 2016; Paolucci et al., 2019), and remission from depression is associated with improvement in ADL (Chemerinski et al., 2001). Further, stroke survivors with depression are less likely to participate in leisure, social and household activities at 3 months (Tse, 2017a) and 12 months (Tse, 2019). Post-stroke depression has been shown to be associated with lower return to work rates (Artwert et al., 2017; Van der Kemp et al., 2017). In addition, stroke survivors with depression who do attain some degree of recovery are slower to achieve this, than those without depression (Chemerinksi et al., 2001; Prisnie et al., 2016; Astuti et al., 2020). Compared to stroke survivors without depression, stroke survivors with depression are likely to experience overall poorer quality of life (Kwok et al., 2006).

It is important to highlight that the association between post-stroke depression and recovery does not occur in isolation from other factors. Poor recovery outcomes may occur not solely due to post-stroke depression, but also due to the combination of depression with other variables, including psychosocial and contextual factors (Gainotti, 2001). Other factors known to influence recovery following stroke include the severity of the stroke (Rost et al., 2016), older age (Knoflach et al., 2012) and female sex (Bushnell et al., 2014).

1.4 Thesis Aims and Research Questions

1.4.1 Primary aims

The primary aims of this thesis are:

- To explore the trajectory of post-stroke depression over time, and
- To explore the association of post-stroke depressive symptoms and recovery outcomes following stroke.

1.4.2 Research questions

To achieve these primary aims, the following five research questions have been developed, and are addressed in the subsequent chapters of this thesis.

1. What is the trajectory of depressive symptoms following stroke over time?

This question is addressed in the Review (Chapter 2) and in Empirical Research Study 1 (Chapter 5).

2. What are the associations between the presence of depressive symptoms at earlier time points with their presence at later time points?

This question is addressed in Empirical Research Study 1 (Chapter 5).

3. What is current Australian clinical practice regarding screening for post-stroke depression?

This question is addressed in Empirical Research Study 1 (Chapter 5) and in the Perspective Article (Chapter 6).

4. What is the association between depressive symptoms and recovery, over the first year following stroke, using a profile of recovery outcome measures?

This question is addressed in Empirical Research Study 2 (Chapter 7).

5. What is the association between comorbidity burden and patient perceived recovery outcomes within the first year post-stroke?

This question is addressed in Empirical Research Study 3 (presented in Chapter 8).

Chapter 2.

Review: Trajectory of Depressive Symptoms Following Stroke

This chapter presents a comprehensive review of longitudinal cohort studies that evaluate depression or depressive symptoms following stroke, at two or more time points. This review identifies and characterises all relevant studies, in order to better understand the trajectory of post-stroke depression. There are five sections in this chapter, as follows:

- 2.1 Introduction
- 2.2 Methodology
- 2.3 Results
- 2.4 Discussion
- 2.5 Conclusion

Trajectory of Depressive Symptoms Following Stroke: A Review of Longitudinal Cohort Studies.

2.1 Introduction

Depression is a common sequela of stroke (Ayerbe et al., 2013a; Hackett & Pickles, 2014). The point prevalence of post-stroke depression has been reported to be 31 per cent (95% CI [28, 35]) within the first five years (Hackett & Pickles, 2014) and 29 per cent (95% CI [25, 32]) during the first 10 years (Ayerbe, et al. 2013a) following stroke. The term 'point prevalence' refers to the proportion of individuals with a condition of interest, in a given population, at a specific point in time. The term 'period prevalence' is similar but refers to a specified period of time (Centres for Disease Control and Prevention [CDC], 2012). When the term 'prevalence' is reported without further description, it is usually interpreted as indicating point prevalence (Habibzadeh & Habibzadeh, 2020). Point prevalence is an epidemiological measure of disease frequency and is often used for chronic diseases with dates of onset that can be difficult to determine (CDC, 2012). Further, point prevalence reflects the importance and health burden of conditions (Habibzadeh & Habibzadeh, 2020) – such as post-stroke depression.

Despite the known high prevalence of post-stroke depression, there is a relative lack of understanding concerning its trajectory. Among stroke survivors, depression appears to have a dynamic trajectory, with new cases of depression, and recovery from depression, occurring over time (Ayerbe et al., 2013b; Das & Rajanikant, 2018). The term 'trajectory', in the context of post-stroke depression, comprises the following temporal characteristics: the timing of onset, the

course, and the duration of depressive symptoms. In regard to the timing of onset, most episodes of depression begin within the first year, with one-third identified during the first three months (Ayerbe et al., 2013b). For the remaining two-thirds, however, depression does not emerge for many months, or even years, following stroke (Ayerbe et al., 2013b). The course of post-stroke depression may be episodic or persistent (Mitchell, 2016). The duration of post-stroke depression can refer either to the duration of individual episodes in a recurring course, or to the total duration of post-stroke depression until complete resolution.

Townend and colleagues highlighted the importance of research exploring the course of depression in the acute ("2 to 5 days") and subacute ("1 month" and "3 months") phases following stroke (Townend et al., 2007, p. 430). These authors recommended further research into the dynamic nature of depressive symptoms in the stroke population to improve understanding of the condition (Townend et al., 2007). The meta-analyses conducted by Hackett and Pickles (2014) and Ayerbe et al. (2013a) also demonstrated its dynamic trajectory – and further, that post-stroke depression extends beyond three months and into chronic phases. Longitudinal studies with assessments of post-stroke depression, at multiple time points beyond the subacute phase, can provide insight into changes in depression and depressive symptoms over time. This information would further our understanding of the trajectory of post-stroke depression and provide insight into its detection and subsequent management. Accordingly, the aim of this review was to identify and characterise longitudinal cohort studies that assess depression or depressive symptoms, at two or more time points following stroke, in order to better understand the trajectory of post-stroke depression.

2.2 Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The review protocol was prospectively registered with the international Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42020189598. The stages of this review included: development of the search strategy; title and abstract screening; full-text screening; extraction of relevant data; and analysis of data.

2.2.1 Search strategy

A comprehensive, concept-based search strategy was developed, in collaboration with a research librarian, to identify all relevant observational cohort studies. The search strategy was applied across four databases: Medline 1946- (Ovid), PsycINFO 1806- (Ovid), Embase 1947- (Classic) and CINAHL 1961- (EBSCOhost). Each database was searched from inception to 31 July 2020; a subsequent search updated this strategy to 4 August 2021.

Three key concepts were identified: ‘stroke’, ‘depression’ and ‘trajectory’. Search terms for each concept comprised subject headings (controlled or index terms) and key words (free-text terms), presented in Table 2.1. Subject headings were modified, as required, for translation across databases; key words were used consistently. All subject headings were also searched as key words. The search syntax performed for each database is presented in Appendix A. There were no limitations imposed on the search. The studies retrieved from the search strategy applied to each of the four databases were imported into Covidence (Veritas Health Innovation, 2021) – a web-based software management platform used to streamline the production of systematic reviews. Removal of duplicate studies occurred prior to title and abstract screening.

Table 2.1

Search Terms, by Concept

Concept 1 Depression	
Subject headings	**Key words**
Depression	depress*
Depression (Emotion)	depress* symptom*
Post-stroke depression	post stroke depress*
	PSD
Concept 2 Stroke	
Subject headings	**Key words**
Brain infarction	brain infarct*
Brain ischemia	brain isch*mia
Cerebral hemorrhage	cerebral h*morrhage
Cerebral infarction	cerebral infarct*
Cerebral ischemia	cerebral isch*mia
Cerebral stroke	cerebral stroke
Cerebrovascular accident	cerebrovascular accident
Cerebrovascular accidents	cerebrovascular disease
Cerebrovascular disease	cerebrovascular disorder
Cerebrovascular disorder	cerebrovascular stroke
Cerebrovascular disorders	CVA
Cerebrovascular stroke	h*morrhagic stroke
Stroke	isch*mic stroke
	stroke
Concept 3 Trajectory	
Subject headings	**Key words**
Longitudinal Studies	course$
Longitudinal Study	longitudinal stud*
	longitudinal
	over time
	trajector*

2.2.2 Study eligibility

Definitions, inclusion criteria and exclusion criteria were developed to establish study eligibility, prior to title and abstract screening.

Definitions

Stroke is defined by the World Health Organisation (WHO) as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" (Aho et al., 1980, p. 114). In this review, 'post-stroke depression' was defined as either the presence of 'depressive symptoms' or the diagnosis of 'depression' following stroke. The presence of depressive symptoms was defined by a score above a threshold on a validated measure for depressive symptoms. A score above a threshold indicates the possible or likely presence of depression – but on its own is not diagnostic of depression. The diagnosis of depression was defined by the clinical diagnosis of minor or major depression according to the Diagnostic Statistical Manual (DSM). Post-stroke depression is classified in the DSM-5 within the category: 'mood disorders due to another medical condition' (American Psychiatric Association [APA], 2013a). A diagnosis of post-stroke depression requires a comprehensive psychiatric interview conducted by a trained practitioner, to assess for the presence of specific criteria outlined in the DSM (Mitchell, 2016).

Inclusion criteria

The inclusion criteria developed for this review were as follows:

- original, full-text studies with primary data, written in English and published in peer-reviewed journals
- longitudinal, observational cohort studies comprising adult human stroke survivors (at least 18 years of age)
- studies that comprised participants with first or recurrent strokes
- studies that comprised participants with ischaemic, haemorrhagic or mixed stroke types, clinically confirmed by a neurologist or by relevant imaging techniques, such as computer tomography (CT) or magnetic resonance imaging (MRI)
- studies that prospectively recruited participants and retained at least 10 participants by the last assessment time point
- studies that assessed depression, or depressive symptoms using a validated measure, at two or more assessment time points
- studies that reported outcome data as either:
    a) a frequency, number, or proportion of participants with depression, using DSM criteria for minor or major depression
    b) a frequency, number, or proportion of participants with depressive symptoms, using a specified cut-off score on a validated measure

c) a sample mean score, and associated standard deviation, of depressive symptoms on a validated measure

Exclusion criteria

The exclusion criteria for this review were as follows:

- qualitative studies, pilot studies, intervention studies and dissertations
- studies published only in abstract form without available full text, including conference proceedings
- studies that comprised participants with unconfirmed, self-reported or proxy-reported stroke, not clinically confirmed by a neurologist nor by medical imaging
- studies that exclusively comprised participants with strokes other than ischaemic or haemorrhagic types, such as transient ischaemic attack (TIA) or subarachnoid haemorrhage (SAH)
- studies that assessed depression or depressive symptoms experienced only by the caregivers or spouses of stroke survivors
- studies that comprised a selected cohort of stroke survivors who already had established diagnoses of depression
- studies with samples of participants with different neurological conditions, from which data pertaining to stroke patients could not be separately extracted
- studies that reported outcome data relating to depression or depressive symptoms that could not be extracted nor extrapolated into the result types required for this review
- studies that reported outcome data obtained from a cohort that had been reported in another study already included in this review
- studies with a primary aim relating to the assessment of psychometric properties or clinical utility of a measure of depression or depressive symptoms

Eligibility criteria relating to assessment time points

During full-text screening, it was noted that there was considerable latitude in the reported descriptions of assessment time points post-stroke. Accordingly, further criteria pertaining to assessment times points were developed to facilitate the precise evaluation of depression after stroke onset, over time (Figure 2.1). These criteria were adopted; their description and rationale are summarised in the following paragraphs.

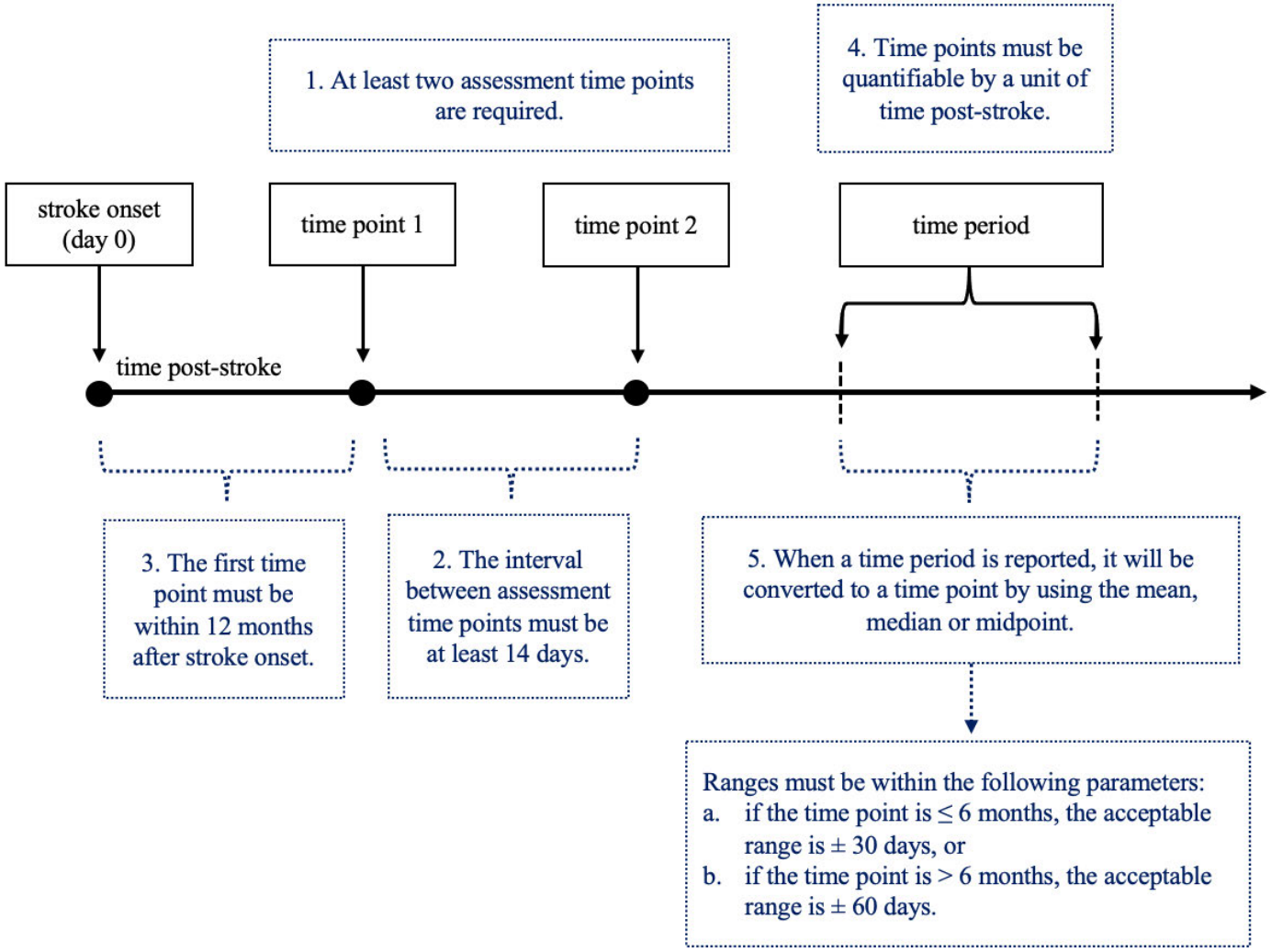
First, at least two assessment time points would be required, in order to characterise a trajectory of post-stroke depression. Second, the interval between assessment time points must be at least 14 days. This criterion aligns to the conditions set by screening measures and diagnostic assessment. To meet the threshold on a screening measure, depressive symptoms are assessed over a preceding time period of either one week (for example, when using the MADRS SIGMA or CES-

D) or two weeks (for example, when using the BDI or PHQ). Similarly, to fulfil the criteria of depression using the DSM, symptoms must be persistent and experienced over at least the preceding two weeks (APA, 2013a). Third, the first time point studied must be less than 12 months following stroke onset. Fourth, assessment time points must be quantifiable by a unit of time (for example, days, weeks, months or years) after stroke onset, and not solely expressed in relation to a clinical event (such as, 'on admission', 'following discharge', 'at enrolment into the rehabilitation program', or 'at recruitment into the study'). The use of a specific, universally consistent and quantifiable unit of time enables the comparison of studies across different authors, countries of origin and era. Fifth, when a study reports a 'time period' it must be converted to a time point, in order to achieve reasonable precision in measuring trajectories. This will be undertaken by using the mean or median, if reported; or, if not reported, by using the midpoint (the middle of the range). However, for the mean, median or midpoint to be accepted, ranges must be within the following parameters:

a. if the mean, median or midpoint time point is ≤ 6 months post-stroke, the acceptable range is ± 30 days, or
b. if the mean, median or midpoint time point is > 6 months post-stroke, the acceptable range is ± 60 days.

Figure 2.1

Eligibility Criteria Relating to Assessment Time Points



2.2.3 Screening

Title and abstract screening was undertaken independently by two authors (KS and TT) using Covidence (Veritas Health Innovation, 2021). Studies were excluded if they were not relevant, did not meet the inclusion criteria, or if they exhibited any of the exclusion criteria. Studies that appeared to meet the inclusion criteria, and did not clearly demonstrate any of the exclusion criteria, were accepted into the subsequent phase of the screening. Conflicts were resolved through discussion between the two authors who independently undertook the title and abstract screening (KS and TT).

Full-text screening was undertaken independently by two authors (KS and TT). When the full text of a study was not available via the electronic databases, the study's corresponding author was contacted with a request for the full text. These studies were excluded if no response was received within one month. Conflicts were resolved through discussion between the two authors who independently undertook the full-text screening (KS and TT), and with a third author (LMC) when required to achieve consensus.

During full-text screening, studies that reported outcome data from a cohort that had also been reported in another study were identified as 'repeated cohorts'. To avoid duplication of extracted data, two authors (KS and TT) independently reviewed the full texts of these overlapping studies, then collaboratively determined the study most suitable for inclusion. This decision was based on the following factors:

- the largest number of assessment time points post-stroke
- the longest duration of the total study period
- the largest sample size
- the greatest amount of detail in relation to demographic, clinical and outcome data

2.2.4 Data extraction

A standardised spreadsheet was developed and used to extract relevant data from the included studies. The data extracted were categorised into three groups of variables: study detail and design; demographic and clinical characteristics; and outcome data. The full list of variables extracted is presented in Appendix B. Data was independently extracted by three authors (KS, JS and JPS). One author (KS) extracted data from all studies; another author (JS) extracted data from 78 per cent of studies and a third author (JPS) extracted data from 22 per cent of studies. All three authors (KS, JS and JPS) independently extracted data from 13 per cent of studies. Last, extracted data was manually checked by two authors (KS and JS). Inconsistencies and conflicts were resolved through collaborative review of the studies from which discrepancies in extracted data had been identified.

If more than one measure of depressive symptoms was used within one cohort, the outcome data for only one measure was selected, by consensus, for inclusion. When required, data was extrapolated into a value suitable for entry into the data extraction spreadsheet, if this was possible. For example, when studies separately reported proportions of major and minor depression, these proportions were added to yield a single frequency of depression.

Further, some studies only reported the standard error of the mean, rather than the standard deviation. Accordingly, the standard deviation was calculated by multiplying the standard error by the square root of the sample size (Cochrane Collaboration, 2011). In addition, some studies only reported confidence intervals in lieu of standard deviations. The 95% confidence interval (95% CI) was first transformed to the standard error, by dividing the span of the 95% CI by 3.92 (twice the z-value for 0.95 probability). This was multiplied by the square root of the sample size to obtain the standard deviation (Cochrane Collaboration, 2011). For studies that reported results as frequency, the 95% CI was calculated, for each time point. The formulae used for these three calculations are presented in Appendix C.

One further example of actions undertaken to obtain accurate data in the correct format arose from one study that appeared to contain a misprint in their results (Hu et al., 2020). In the methodology section of this paper, the authors stated that normally distributed data were described by means and standard deviations. However, the results table subheading stated that values were reported as means and standard errors. The calculation to transform a standard error to a standard deviation produced large values that did not appear to be consistent with standard deviations. The corresponding author of this study was contacted; their response confirmed there had been a misprint and that the published results were in fact standard deviations.

Categorisation of time points into post-stroke phases

It was observed that there was substantial variation in the assessment time points used across the included studies. Accordingly, assessment time points were categorised into broader post-stroke phases in order to facilitate comparison of depression trajectories between studies. The definitions of the phases utilised in this review were based on key post-stroke phases described in a recovery framework developed by the Stroke Recovery and Rehabilitation Roundtable (SRRR); this framework is underpinned by knowledge of the biology of stroke recovery (Bernhardt et al., 2017).

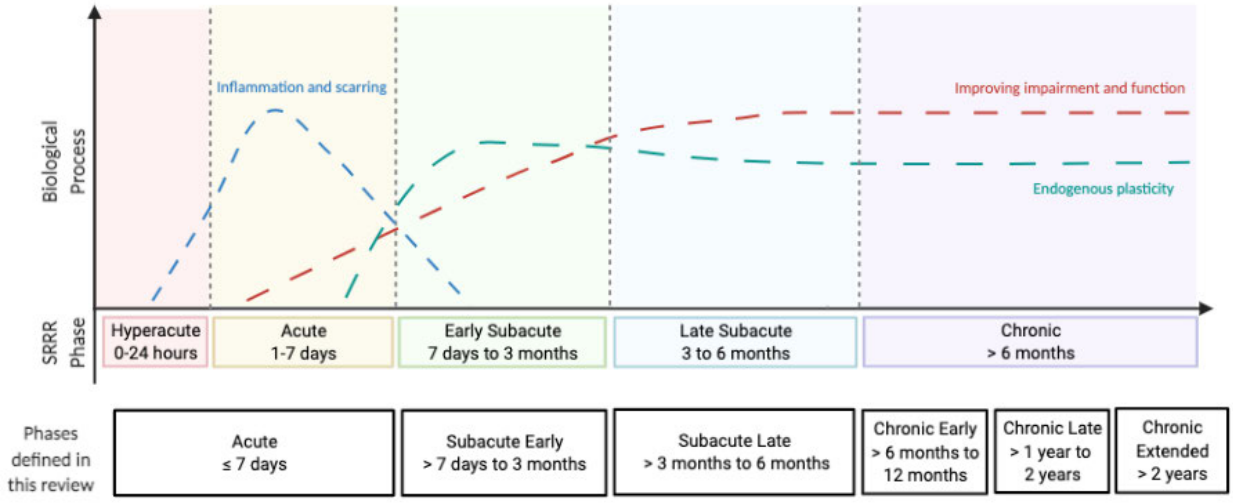
In this review, each assessment time point was categorised into one of six post-stroke phases, illustrated in Figure 2.2 and defined as follows:

- acute (≤ 7 days)
- subacute early (> 7 days to 3 months)
- subacute late (> 3 months to 6 months)

- chronic early (> 6 months to 12 months)
- chronic late (> 12 months to 2 years)
- chronic extended (> 2 years)

Figure 2.2

Categorisation of Time Points into Post-Stroke Phases



Note. This figure has been adapted from Figure 1 in Bernhardt et al. (2017), which depicts post-stroke phases that link to the currently known biology of recovery, developed by the Stroke Recovery and Rehabilitation Roundtable (SRRR). Figure included with permission from SAGE publishing.

2.2.5 Data analysis

The included studies reported results as a frequency or as a mean score – or as both. Characteristics of the studies, characteristics of the cohorts and outcome data pertaining to depression were summarised and tabulated, according to result type. Within each result type, subgroups of studies that all utilised the same measure of depression or depressive symptoms were explored. Outcome data for selected subgroups were presented graphically, using line graphs to facilitate the examination of temporal patterns of post-stroke depression.

2.3 Results

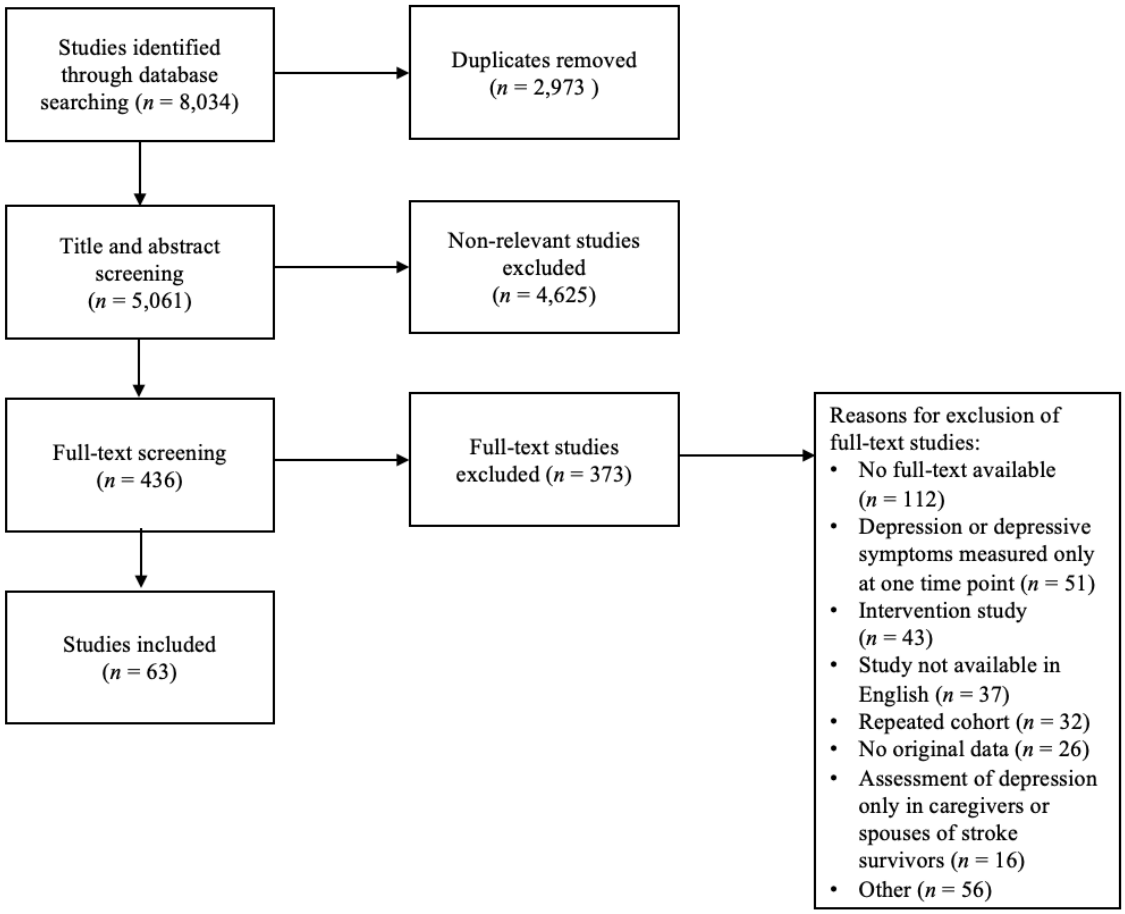
2.3.1 Study selection

The systematic search (from inception to 4 August 2021) yielded 8,034 studies across the four databases. Following the removal of duplicates, 5,061 unique citations were imported for title and abstract screening. After title and abstract screening, 436 studies were eligible for full-text screening. Of these, 63 studies were included for analysis in this review (Figure 2.3). Common reasons for exclusion were as follows: studies with only one assessment time point; intervention studies; conference proceedings and abstracts for which full text was unavailable; studies with

assessment time points described solely by clinical events; studies that assessed depression only in caregivers or spouses of stroke survivors; and studies that evaluated other associated constructs, such as ‘psychological distress’, ‘suicidal ideation’, ‘apathy’ and ‘negative emotions’.

Figure 2.3

PRISMA Flowchart of Study Selection



Note. n refers to the number of studies

2.3.2 Study characteristics

A total of 63 studies were included in this review. There were 44 studies that reported results as frequencies and 33 studies that reported results as mean scores. Accordingly, two separate analyses were undertaken, one for each type of result. Of the 63 studies, 14 presented both frequencies and mean scores, thereby providing results for each of the two analyses. Two studies (Brodaty et al., 2007; Brodaty et al., 2013) comprised participants from the same cohort (Sydney Stroke Study); however, both studies were included because each study reported a different type of result. Brodaty et al. (2007) presented results by frequency and Brodaty et al. (2013) presented results by mean score. There was no duplication of data because each of these studies was allocated separately to the appropriate analysis.

2.3.3 Characteristics of studies that reported frequencies (*n* = 44)

Study design and sample characteristics (Table 2.2)

A total of 44 studies included in this review reported frequency of depression, or depressive symptoms, at each time point. Study design and sample characteristics are presented in Table 2.2. The sample size at baseline of the studies ranged from 20 participants (Iacoboni et al., 1995) to 2,477 participants (White et al., 2011). Sixteen studies were parts of larger cohorts. All studies were published from the year 1990 to 2021 inclusive; most (27/44, 61.4%) were published from 2011 to 4 August 2021. The studies were conducted across 22 different nations. Six were undertaken in the United States of America, four each in Australia and Germany, and three each in The Netherlands, Norway and China. One study (DeWit et al., 2008) collected data across four European countries (Belgium, United Kingdom, Switzerland and Germany); this study was categorised as having been conducted in Europe. Twenty-one studies (21/44, 47.7%) comprised cohorts of participants with ischaemic stroke only. Twenty studies (20/44, 45.5%) described cohorts of participants with mixed stroke types, both ischaemic and haemorrhagic. For the remaining three studies (3/44, 6.8%), the stroke type was not reported. Thirty studies (30/44, 68.2%) included participants with first or recurrent strokes. The remaining 14 studies (14/44, 31.8%) comprised only participants with their first stroke (Table 2.2).

Table 2.2

Studies Reporting Post-Stroke Depression or Depressive Symptoms by Frequency (n = 44)

Study Author, year, country [cohort acronym or name]	**Type of stroke**	**First or recurrent stroke**	**Age mean (*SD*)** [or range, *Mdn*, IQR if *M* was not reported]	**Female sex %**	**Measure and cut off score**	**Post-stroke phase**	**Assessment time point post-stroke**	**Number assessed (*n*)**	**Frequency (%)**	**95% CI (%)**
Aben et al. (2003) Netherlands	ischaemic	first	68.60 (11.70)	46.80	DSM-IV major or minor	subacute early	30 days	190	21.58	(16.63, 28.53)
						subacute early	90 days	138	5.07	(1.41, 8.73)
						subacute late	180 days	117	5.98	(1.68, 10.28)
						chronic early	270 days	107	5.61	(1.25, 9.97)
						chronic late	365 days	98	7.14	(2.04, 12.24)
Allan et al. (2013) United Kingdom [COGFAST]	mixed	first or recurrent	80.00 (4.10)	48.17	DSM-IV major only	subacute early	90 days	342	1.17	(0.03, 2.31)
						chronic early	365 days	270	0.37	(0.00, 1.09)
						chronic late	730 days	226	0.44	(0.00, 1.30)
						chronic extended	1,095 days	183	4.92	(1.79, 8.05)
						chronic extended	1,460 days	149	2.68	(0.09, 5.27)
						chronic extended	1,825 days	119	0.84	(0.00, 2.48)
						chronic extended	2,190 days	105	13.33	(6.83, 19.83)
						chronic extended	2,555 days	73	9.59	(2.84, 16.34)
						chronic extended	2,920 days	42	19.05	(7.17, 30.93)
						chronic extended	3,285 days	33	12.12	(0.99, 23.25)
						chronic extended	3,650 days	15	20.00	(0.00, 40.24)
Astrom et al. (1993) Sweden	mixed	first or recurrent	73.00 range: 44, 100	38.75	DSM-III major only	acute	4.5 days	76	25.00	(15.26, 34.74)
						subacute early	90 days	73	31.51	(20.85, 42.17)
						chronic early	365 days	68	16.18	(7.43, 24.93)
						chronic late	730 days	57	19.30	(9.05, 29.55)
						chronic extended	1,095 days	49	28.57	(15.92, 41.22)
Ayerbe et al. (2013) United Kingdom [SLSR]	mixed	first	not reported	46.00	HADS-D ≥ 8	subacute early	90 days	1,101	32.79	(30.02, 35.56)
						chronic early	365 days	1,233	28.95	(26.42, 31.48)
						chronic late	730 days	901	29.52	(26.54, 32.50)
						chronic extended	1,095 days	1,100	30.91	(28.18, 33.64)
						chronic extended	1,460 days	890	30.11	(27.10, 33.12)
						chronic extended	1,825 days	658	29.48	(26.00, 32.96)
						chronic extended	2,190 days	600	29.83	(26.17, 33.49)
						chronic extended	2,555 days	475	31.79	(27.60, 35.98)
						chronic extended	2,920 days	392	28.83	(24.35, 33.31)
						chronic extended	3,285 days	296	35.81	(30.35, 41.27)
						chronic extended	3,650 days	234	34.62	(28.52, 40.72)
						chronic extended	4,015 days	183	29.51	(22.90, 36.12)
						chronic extended	4,380 days	116	31.90	(23.42, 40.38)
						chronic extended	4,745 days	72	38.89	(27.63, 50.15)
						chronic extended	5,110 days	46	30.43	(17.13, 43.73)
						chronic extended	5,475 days	16	31.25	(8.54, 53.96)

Baccaro et al. (2019) Brazil [EMMA]	mixed	first or recurrent	62.00 (12.30)	43.00	PHQ-9 ≥ 10	subacute late chronic late	180 days 730 days	100 100	15.00 19.00	(8.00, 22.00) (11.31, 26.69)
Bacher et al. (1990) Canada	not reported	first or recurrent	71.00 (10.20)	39.58	ZSRD ≥ 50	subacute early subacute late chronic early chronic late	57.3 days 99.3 days 237.3 days 422.3 days	48 43 42 49	29.17 34.88 40.48 40.82	(16.31, 42.03) (20.64, 49.12) (25.64, 55.32) (27.06, 54.58)
Bae et al. (2019) South Korea	ischaemic	first or recurrent	64.70 (10.00)	41.91	DSM-IV major or minor	subacute early chronic early	14 days 365 days	408 284	25.25 26.06	(21.03, 29.47) (20.95, 31.17)
Barker-Collo et al. (2016) New Zealand [ARCOS-IV]	ischaemic	first or recurrent	70.89 (14.11)	47.00	HADS-D ≥ 9	subacute early subacute late chronic early	30 days 180 days 365 days	367 365 386	10.08 9.04 9.33	(7.00, 13.16) (6.10, 11.98) (6.43, 12.23)
Berg et al. (2003) Finland	ischaemic	first	55.20 (10.60)	32.00	BDI ≥ 10	subacute early subacute early subacute late chronic early chronic late	14 days 60 days 180 days 365 days 540 days	89 92 90 88 85	26.97 29.35 23.33 23.86 25.88	(17.75, 36.19) (20.05, 38.65) (14.59, 32.07) (14.95, 32.77) (16.57, 35.19)
Brodaty et al. (2007) Australia [Sydney Stroke Study]	ischaemic	first or recurrent	72.10 (8.70)	42.96	DSM-IV major or minor	subacute late chronic late	135 days 455 days	135 134	14.07 21.64	(8.20, 19.94) (14.67, 28.61)
De Ryck et al. (2014) Belgium [MISS]	mixed	first or recurrent	70.10 (13.10)	42.79	CDS ≥ 8	subacute early subacute early subacute late chronic early chronic late	30 days 90 days 180 days 365 days 545 days	94 170 99 116 156	24.47 27.06 28.28 19.83 26.28	(15.78, 33.16) (20.38, 33.74) (19.41, 37.15) (12.57, 27.09) (19.37, 33.19)
De Wit et al. (2008) Europe [CERISE]	mixed	first or recurrent	69.50 (10.30)	46.73	HADS-D ≥ 8	subacute late subacute late subacute late	60 days 120 days 180 days	491 478 467	27.70 31.38 26.12	(23.74, 31.66) (27.22, 35.54) (22.14, 30.10)
Dong et al. (2021) United States [BASIC]	mixed	first or recurrent	65.80 (11.20)	50.62	PHQ-8 ≥ 10	subacute early subacute late chronic early	90 days 180 days 365 days	648 542 533	35.34 24.91 25.70	(31.66, 39.02) (21.27, 28.55) (21.99, 29.41)
dos Santos et al. (2018) Brazil	mixed	first or recurrent	70.30 (7.60)	50.00	GDS-15 ≥ 6	subacute early subacute late chronic early	20.6 days 96.6 days 200.6 days	50 50 50	30.00 24.00 38.00	(17.30, 42.70) (12.16, 35.84) (24.55, 51.45)
Douven et al. (2018) Netherlands [CASPER]	mixed	first or recurrent	67.31 (11.80)	34.58	DSM-IV major or minor	subacute early chronic early chronic late	87 days 270 days 455 days	240 211 217	10.83 14.22 11.06	(6.90, 14.76) (9.51, 18.93) (6.89, 15.23)
El Husseini et al. (2017) United States [AVAIL]	ischaemic	first or recurrent	median: 64 Q1, Q3: 55, 74	44.10	PHQ-8 ≥ 10	subacute early chronic early	90 days 365 days	1,444 1,444	18.01 16.41	(16.03, 19.99) (14.50, 18.32)

Eriksen et al. (2016) Norway [Post-Stroke Fatigue Study]	mixed	first	67.70 (13.00)	41.49	BDI ≥ 14	acute chronic early chronic late chronic late	7.5 days 187.5 days 372.5 days 552.5 days	94 94 94 94	28.72 28.72 23.40 26.60	(19.57, 37.87) (19.57, 38.87) (14.84, 31.96) (17.67, 35.53)
Fuentes et al. (2009) Spain	ischaemic	first or recurrent	66.70 (10.60)	31.76	HDRS ≥ 8	acute subacute early	5 days 90 days	85 59	9.41 28.81	(3.20, 15.62) (17.25, 40.37)
Hu et al. (2020) China	mixed	first	not extrapolatable	29.23	PHQ-9 ≥ 5	subacute early subacute early	30 days 90 days	65 65	24.62 18.46	(14.15, 35.09) (9.03, 27.89)
Hung et al. (2012) Taiwan	ischaemic	first or recurrent	66.10 Q1, Q3: 59, 74	46.07	BDI ≥ 10	subacute early subacute late	90 days 180 days	89 89	58.43 57.30	(48.19, 68.67) (47.02, 67.58)
Iacoboni et al. (1995) Italy	ischaemic	first	52.90 (8.80)	40.00	RDI [a]	subacute early chronic late	15 days 380 days	20 20	55.00 35.00	(33.20, 76.80) (14.10, 55.90)
Kauhanen et al. (2000) Finland	ischaemic	first	65.80 (11.89)	43.40	DSM-III-R major or minor	subacute early subacute late	90 days 180 days	101 92	18.81 14.13	(10.66, 25.70) (7.01, 21.25)
Kawasaki & Hoshiyama (2020) Japan	mixed	first	69.10 (12.40)	30.95	ZSRD ≥ 50	subacute early subacute early	31.6 days 90 days	42 42	16.67 16.67	(5.40, 27.94) (5.40, 27.94)
Kim et al. (2014) South Korea	ischaemic	first or recurrent	64.50 (10.00)	42.32	DSM-IV major or minor	subacute early chronic late	12.3 days 396 days	423 288	25.53 26.04	(21.37, 29.69) (20.97, 31.11)
Ladwig & Werheid (2020) Germany	ischaemic	first or recurrent	63.60 (10.90)	40.26	DSM-5 major or minor	subacute early chronic early chronic late	42 days 276 days 483 days	303 196 181	36.63 32.14 25.97	(31.21, 42.05) (25.60, 38.68) (19.58, 32.36)
Lai et al. (2002a) United States [Kansas City Stroke Study]	mixed	first or recurrent	70.00 (11.40)	53.38	GDS-15 ≥ 6	subacute early subacute early subacute early subacute late	8.5 days 30 days 90 days 180 days	398 395 372 352	33.17 35.19 34.14 30.11	(28.54, 37.80) (30.48, 39.90) (29.32, 38.96) (21.39, 30.55)
Liang et al. (2018) Hong Kong	ischaemic	first or recurrent	67.00 (10.20)	40.85	GDS-15 ≥ 7	subacute early chronic early chronic late	90 days 270 days 455 days	563 458 563	18.29 11.57 12.26	(15.10, 21.48) (8.64, 14.50) (9.55, 14.97)
Lopatkeiwicz et al. (2021) Poland [PROPOLIS]	ischaemic	first or recurrent	median: 68	48.36	PHQ-9 ≥ 10	subacute early subacute early	8 days 90 days	335 335	22.69 24.18	(18.21, 27.17) (19.59, 28.77)
Morsund et al. (2019) Norway	ischaemic	first or recurrent	58.00 (10.00)	37.04	HADS-D ≥ 8	subacute early chronic early	90 days 365 days	324 287	8.95 12.20	(5.84, 12.06) (8.41, 15.99)
Ormstad et al. (2012) Norway	ischaemic	first	67.70 (11.80)	40.00	BDI ≥ 10	subacute early chronic early chronic late	180 days 365 days 545 days	45 45 45	64.44 53.33 55.56	(50.45, 78.43) (38.75, 67.91) (41.04, 70.08)

Paradiso et al. (1997) United States	not reported	first or recurrent	not extrapolatable	22.54	HDRS-17 [b]	subacute early	90 days	76	38.16	(27.24, 49.08)
						subacute late	180 days	79	39.24	(28.47, 50.01)
						chronic early	365 days	69	28.99	(18.28, 39.70)
						chronic late	545 days	66	37.88	(26.18, 49.58)
Robinson-Smith et al. (2000) United States	mixed	first or recurrent	71.00 range: 36, 92	44.44	CESD ≥ 16	subacute early	30 days	63	25.40	(14.65, 36.15)
						subacute late	180 days	63	15.87	(6.85, 24.89)
Schepers et al. (2009) Netherlands	mixed	first	56.30 (10.70)	39.70	CESD ≥ 16	subacute late	180 days	131	23.66	(16.38, 30.94)
						chronic early	365 days	131	25.19	(17.76, 32.62)
						chronic extended	1,095 days	131	16.03	(9.75, 22.31)
Schöttke et al. (2020) Germany	ischaemic	first or recurrent	67.51	50.00	DSM-IV major only	subacute early	45.71 days	174	32.18	(25.24, 39.12)
						chronic extended	1170.60 days	84	36.90	(26.58, 47.22)
Shi et al. (2014) China [PRIOD]	ischaemic	first	61.50 (11.50)	35.24	DSM-IV major or minor [c]	subacute early	14 days	1,067	28.40	(25.69, 31.11)
						subacute early	90 days	1,067	20.62	(18.19, 23.05)
						subacute late	180 days	1,067	15.56	(13.39, 17.73)
						chronic early	365 days	1,067	14.43	(12.32, 16.54)
Sit et al. (2007) Hong Kong	mixed	first	67.00 (10.67)	48.42	CESD ≥ 16	acute	6.98 days	112	68.75	(60.17, 77.33)
						chronic early	1.86 days	95	48.42	(38.37, 58.47)
Townend et al. (2007) Australia	mixed	first or recurrent	75.60 (13.12)	52.00	HADS-D ≥ 9	acute	2.6 days	125	4.80	(1.05, 8.55)
						subacute early	34 days	112	16.07	(9.27, 22.87)
						subacute late	91 days	105	20.95	(13.17, 28.73)
Tse et al. (2017) Australia [START]	ischaemic	first or recurrent	67.00 (13.00)	33.51	MADRS ≥ 7	subacute early	90 days	185	43.24	(36.10, 50.38)
						chronic early	365 days	166	39.76	(32.32, 47.20)
Verdelho et al. (2004) France [The Lille Stroke/Dementia Cohort]	mixed	first or recurrent	median: 75 range: 42, 101	51.98	MADRS ≥ 7	subacute late	180 days	108	42.59	(33.26, 51.92)
						chronic early	365 days	96	36.46	(26.83, 46.09)
						chronic late	730 days	71	23.94	(14.01, 33.87)
						chronic extended	1,095 days	73	17.81	(9.03, 26.59)
Volz et al. (2021) Germany [Berlin PSD Study]	ischaemic	first or recurrent	63.67 (10.81)	40.20	DSM-5 major or minor	subacute early	51.3 days	301	36.54	(31.10, 41.98)
						chronic early	300.6 days	195	31.79	(25.25, 38.33)
						chronic late	531.2 days	179	25.70	(19.30, 32.10)
						chronic extended	829 days	80	13.75	(6.20, 21.30)
						chronic extended	1,009 days	49	12.24	(3.06, 21.42)
White et al. (2011) United States [SPS3]	ischaemic	first or recurrent	63.20 (10.70)	37.02	PHQ-9 [d]	subacute late	128 days	2,477	19.01	(17.46, 20.56)
						chronic early	365 days	1,934	17.01	(15.34, 18.68)
						chronic late	730 days	1,468	16.01	(14.13, 17.89)
						chronic extended	1,095 days	1,117	16.03	(13.88, 18.18)
						chronic extended	1,460 days	714	13.03	(10.56, 15.50)
White et al. (2014) Australia	mixed	first or recurrent	75.00 (12.00)	55.22	HADS-D ≥ 8	acute	3.5 days	134	22.39	(15.33, 29.45)
						subacute early	90 days	121	28.93	(20.85, 37.01)
						subacute late	180 days	109	22.02	(14.24, 29.80)
						chronic early	270 days	109	28.44	(19.97, 36.91)
						chronic early	365 days	110	20.00	(12.52, 27.48)

Wilz & Barskova (2007) Germany	not reported	first	58.00 range: 40, 83	33.33	CDS ≥ 12	subacute early chronic late	90 days 455 days	81 57	20.99 17.54	(12.12, 29.86) (7.67, 27.41)
Zhou et al. (2020) China	ischaemic	first	62.47 (10.45)	30.41	HADS-D ≥ 8	subacute early subacute early subacute late chronic late	7.54 days 37.54 days 97.54 days 187.54 days	217 215 208 209	21.20 34.42 33.17 29.19	(15.76, 26.64) (28.07, 40.77) (26.77, 39.57) (23.03, 35.35)

Note. M = mean; *Mdn* = median; *SD* = standard deviation; IQR = interquartile range; CI = confidence interval; COGFAST = Cognitive Function After Stroke Study; SLSR = South London Stroke Register; EMMA = "Estudo de Mortalidade E Morbidade Do Acidente Vascular Cerebra" or the Study of Stroke Mortality and Morbidity; ARCOS-IV = Auckland Regional Community Stroke Study; MISS = Middelheim Interdisciplinary Stroke Study; CERISE = Collaborative Evaluation of Rehabilitation in Stroke across Europe, BASIC = Brain Attack Surveillance in Corpus Christi project; CASPER = Cognition and Affect – a Prospective Evaluation of Risks study; AVAIL = Adherence Evaluation After Ischemic Stroke Longitudinal study; PROPOLIS = Prospective Observational Polish study on post-stroke delirium; START = Stroke Imaging Prevention and Treatment; PRIOD = Prospective Cohort Study on the Incidence and Outcome of Patients with PSD; SPS3 = Secondary Prevention of Small Subcortical Strokes. DSM = Diagnostic Statistical Manual of Mental Disorders (APA, 2013a); HADS-D = Hospital Anxiety and Depression Scale – Depression subscale (Zigmond & Snaith, 1983); PHQ = Patient Health Questionnaire (Spitzer et al., 1994; Kroenke et al., 2001); ZSRD = Zung Self Rating Depression scale (Zung, 1965); BDI = Beck Depression Inventory (Beck, 1961); CDS = Cornell Depression Scale (Alexopoulos et al., 1988); GDS = Geriatric Depression Scale (Yesavage et al., 1982); HDRS = Hamilton Depression Rating Scale (Hamilton, 1960); RDI = Rome Depression Inventory (Pancheri & Carilli, 1982); CESD = Center for Epidemiological Studies - Depression (Radloff, 1977); MADRS = Montgomery-Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979).

[a] no cut-off score specified for the RDI. [b] no cut-off score specified for the HDRS-17. [c] Not specified; however, both major and minor depression implied. [d] no cut-off score specified for the PHQ-9; however, authors defined depressive symptoms 'present' as having at least 2 of the 9 symptoms (including both the anhedonia and depressed mood item).

Assessments of depression or depressive symptoms

The 44 studies examined post-stroke depression over periods ranging from 3 months (Fuentes et al., 2009; Kawasaki & Hoshiyama, 2020, 2020; Townend et al., 2007; Hu et al., 2020, Ladwig & Werheid et al., 2020) to 15 years (Ayerbe et al., 2013b) following stroke onset (Table 2.2). All studies had at least two assessment time points, as per eligibility criteria for inclusion in this review; many studies (18/44, 40.9%) comprised only two assessment time points. There were two studies of very long duration; one included 11 time points over 10 years (Allan et al., 2013) and another comprised 16 time points over a 15 year study period (Ayerbe et al., 2013b). Eleven different validated measures of depression or depressive symptoms were employed across the 44 studies. Twelve studies (12/44, 27.3%) used the DSM; 7 studies (7/44, 15.9%) used the Hospital Anxiety and Depression Scale – Depression subscale (HADS-D) and 6 studies (6/44, 13.6%) used the Patient Health Questionnaire (PHQ) (Table 2.2).

2.3.4 Frequencies and trajectories of depression across post-stroke phases for studies that reported frequencies (*n* = 44)

Frequencies and corresponding 95% CIs of depression or depressive symptoms are reported in Table 2.2, at each time point with the corresponding post-stroke phase. Six studies recorded their first assessment in the acute phase (0 to 7 days) post-stroke, with frequencies of depression, or depressive symptoms, ranging from 5 to 69 per cent. Thirty-six studies comprised at least one assessment in the subacute early phase (> 7 days to 3 months), with frequencies of depression ranging from 2 to 64 per cent. Twenty-two studies included at least one assessment in the subacute late phase (> 3 months to 6 months), with frequencies of depression ranging from 6 to 57 per cent. Twenty-seven studies recorded at least one assessment in the chronic early phase (> 6 months to 12 months), with frequencies of depression ranging from less than 1 per cent to 53 per cent. Twenty-two studies comprised at least one assessment in the chronic late phase (more than 12 months to 2 years), with frequencies of depression ranging from less than 1 per cent to 56 per cent. Eight studies included at least one assessment in the chronic extended phase (more than 2 years), with frequencies of depression ranging from less than 1 per cent to 39 per cent (Table 2.2).

Frequencies of Depression Utilising DSM

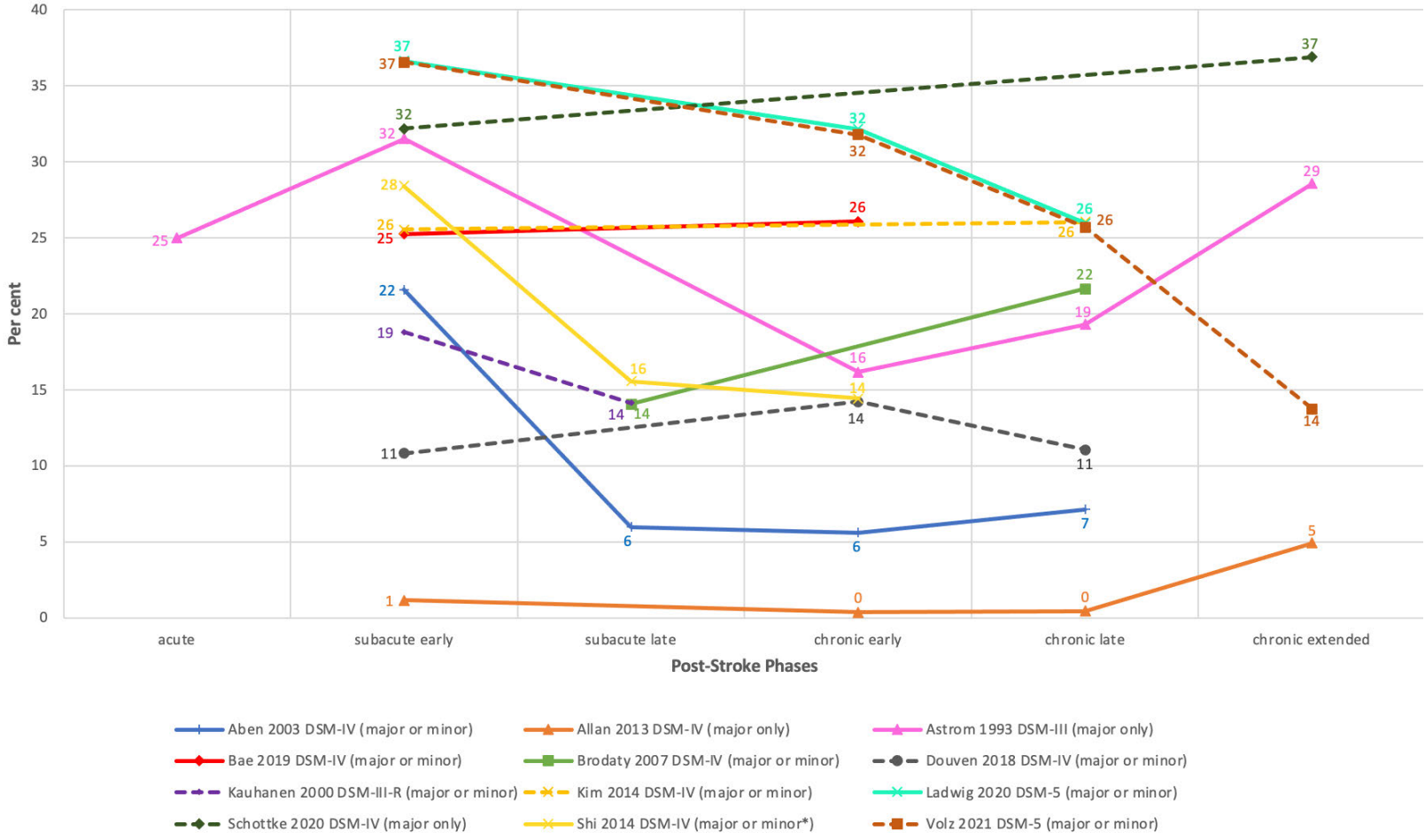
The direct comparison of the frequencies of depression or depressive symptoms across the 44 studies was problematic because of the variety of measures and time points used. Even studies that utilised the same measure of depressive symptoms often used different versions of that measure or different cut-off scores. There were 12 studies that reported frequency of post-stroke depression, as diagnosed by the DSM. Although the DSM has been revised periodically, the core criteria for diagnosing depression across recent iterations have not changed (American Psychiatric Association, 2013b). This consistent approach of evaluating depression enabled the more precise comparison of post-stroke depression trajectories across these 12 studies. Further, focusing on the

use of the DSM was considered to be important because it is the 'gold standard' for diagnosing depression, and against which screening measures are validated. The frequencies and trajectories of depression reported by the 12 studies that utilised the DSM, mapped according to post-stroke phase, are presented in Figure 2.4. For studies that reported frequencies at multiple time points within any one of the post-stroke phases, the time point with the largest sample size was selected.

Considerable variation in the prevalence and the trajectories of post-stroke depression was observed across these 12 studies (Figure 2.4). In the acute phase (0 to 7 days), only one study assessed for depression (Ladwig & Werheid, 2020); 25 per cent of this cohort were diagnosed with depression during this phase. In the subacute early phase (> 7 days to 3 months), most studies assessed for depression; the frequency ranged from 1 per cent (Allan et al., 2013) to 37 per cent (Ladwig & Werheid, 2020 and Volz, 2021). In the subacute late phase (> 3 months to 6 months), the frequency ranged from 6 per cent (Aben et al., 2003) to 16 per cent (Shi et al., 2014). In the chronic early phase (> 6 months to 12 months), the frequency ranged from 0 per cent (Allan et al., 2013) to 32 per cent (Volz et al., 2021; Schöttke et al., 2020). In the chronic late phase (> 12 months to 2 years), the frequency ranged from 0 per cent (Allan et al., 2013) to 26 per cent (Kim et al. 2014; Ladwig & Werheid, 2020; Volz et al., 2021). In the chronic extended phase (> 2 years), the frequency ranged from 5 per cent (Allan et al., 2013) to 37 per cent (Schöttke et al., 2020). Two studies demonstrated trajectories of depression that appeared to remain constant, from 25 to 26 per cent, starting from the subacute early phase through to the chronic early (Bae, 2019) and chronic late (Kim et al., 2014) phases. Another study (Douven et al., 2018) also demonstrated a trajectory that appeared to be relatively constant, but at a lower prevalence between 11 and 14 per cent, from the subacute early phase to the chronic late phase. Four studies showed a declining trajectory of depression over time (Volz et al., 2021; Shi et al., 2014; Ladwig & Werheid, 2020; Kauhanen et al., 2000). Two studies showed a trajectory that appeared to increase over time (Schöttke et al., 2020; Brodaty et al., 2007). One study demonstrated a variable trajectory, with the frequency of depression peaking in the subacute phase, then declining in the chronic early phase, before increasing again in the chronic late and chronic extended phases (Aström et al., 1993). Most studies (9/12, 75.0%) assessed for both major and minor depression; three studies assessed for major depression only (Allan et al., 2013; Schöttke et al., 2020; Aström et al., 1993). These three studies exhibited marked differences in the observed prevalence and trajectories of post-stroke depression.

Figure 2.4

Frequencies and Trajectories of Depression in 12 Studies Utilising DSM, by Post-Stroke Phase



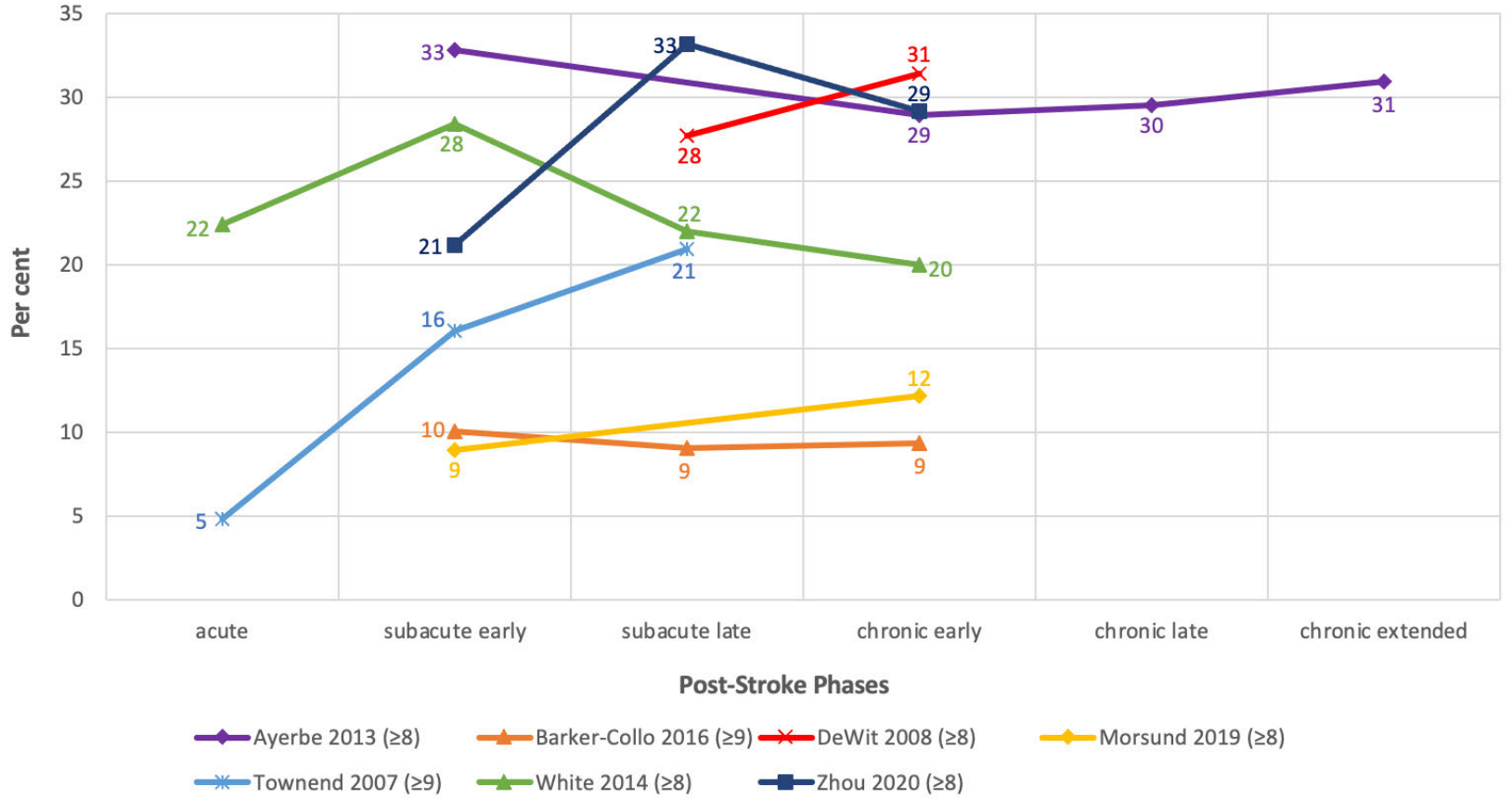
Note. DSM = Diagnostic Statistical Manual of Mental Disorders (APA, 2013a); major = major depression criteria; minor = minor depression criteria.
Post-stroke phases: acute ≤ 7 days; subacute early > 7 days to 3 months; subacute late > 3 months to 6 months; chronic early > 6 months to 12 months; chronic late > 12 months to 2 years; chronic extended > 2 years.

Frequencies of Depression Utilising HADS-D

Of the 10 measures of depressive symptoms employed across the 44 studies, the HADS-D was selected for analysis because it was one of the most commonly used measures and all studies using the HADS-D used the same version. The frequencies of depressive symptoms 'present' reported by the seven studies that utilised the HADS-D, mapped according to post-stroke phase, are presented in Figure 2.5. For studies that reported frequencies at multiple time points within any one of the post-stroke phases, the time point with the largest sample size was selected. The HADS-D subscale comprises seven items; each item is scored from 0 to 3, yielding an overall score ranging from 0 to 21 (Zigmond et al., 1983). Two studies applied a cut-off score ≥ 9 (Barker-Collo et al., 2016; Townend et al., 2007) and the remaining studies applied a cut-off score ≥ 8. Considerable variation in the prevalence and the trajectories of depressive symptoms across these seven studies was observed (Figure 2.5). The assessment time points used were concentrated in the subacute early, subacute late and chronic early phases post-stroke. Across these phases, the prevalence varied from 9 per cent (Morsund et al., 2019; Barker-Collo et al., 2016) to 33 per cent (Ayerbe et al., 2013b; Zhou et al., 2020). Four studies showed trajectories of depressive symptoms that remained relatively constant over time (Barker-Collo et al., 2016; Morsund et al., 2019; Ayerbe et al., 2013b; De Wit et al., 2008). One study demonstrated a trajectory of depressive symptoms that increased from the acute phase to the subacute early and subacute late phases (Townend et al., 2007). Two studies exhibited variable trajectories of depressive symptoms over time (White et al., 2014; Zhou et al., 2020).

Figure 2.5

Frequencies and Trajectories of Depressive Symptoms in 7 Studies Utilising HADS-D, by Post-Stroke Phase



Note. HADS-D = Hospital Anxiety Depression Scale – depression subscale (Zigmond & Snaith, 1983). HADS-D score range: 0 to 21.
Post-stroke phases: acute ≤ 7 days; subacute early > 7 days to 3 months; subacute late > 3 months to 6 months; chronic early > 6 months to 12 months; chronic late > 12 months to 2 years; chronic extended > 2 years.

2.3.5 Characteristics of studies that reported means (*n* = 33)

Study design and sample characteristics

A total of 33 studies included in this review reported the mean scores and associated standard deviations on a measure of depressive symptoms, at each time point (Table 2.3). The sample size at baseline of the studies ranged from 20 participants (Iacoboni et al., 1995) to 1,404 participants (Hjollund, 2017). Eleven studies were parts of larger cohorts. All studies were published from the year 1990 to 2020 inclusive; most (23/33, 69.7%) were published from 2011 to 2020. The studies were conducted across 16 different nations; four were undertaken in each of Australia, Germany and United States of America. Most studies (20/33, 60.6%) described cohorts of participants with mixed stroke types, both ischaemic and haemorrhagic. Ten studies (10/33, 30.3%) comprised cohorts of participants with ischaemic stroke only. Three studies (3/33, 9.1%) did not report the stroke type. Eighteen studies (18/33, 54.5%) included participants with first or recurrent strokes. Fifteen studies (15/33, 45.5%) comprised only participants with their first stroke (Table 2.3).

Assessment of depressive symptoms

The 33 studies examined post-stroke depressive symptoms over periods ranging from three months (Townend et al., 2007; Hu et al., 2020) to five years (Brodaty et al., 2013). All studies had at least two assessment time points, as per eligibility criteria; many studies (14/33, 42.4%) comprised only two assessment time points. One study (Hjollund, 2017) included eight time points over a five year period. Ten different validated measures of depressive symptoms were used across the 33 studies. The Center for Epidemiological Studies – Depression (CES-D) measure was used in seven studies (7/33, 21.2%); the HADS-D was used in six studies (6/33, 18.1%); and the Geriatric Depression Scale (GDS) and Beck Depression Inventory (BDI) were each used by five studies (5/33, 15.2%) (Table 2.3).

Table 2.3

Studies Reporting Post-Stroke Depressive Symptoms by Mean Score (n = 33)

Study Author, year, study acronym or name	**Type of stroke**	**First or recurrent stroke**	**Age mean (*SD*)** [or range, *Mdn*, IQR if *M* was not reported]	**Female sex %**	**Measure**	**Post-stroke phase**	**Assessment time point post-stroke**	**Number assessed (*n*)**	**Mean**	***SD***
Alexander & Wilz (2010) Germany	mixed	first	59.08 (10.47)	31.96	CDS	subacute early chronic late	78 days 438 days	97 80	7.65 7.55	6.48 5.90
Baccaro et al. (2019) Brazil [EMMA]	mixed	first or recurrent	62.00 (12.30)	43.00	PHQ-9	subacute late chronic late	180 days 730 days	100 100	4.00 2.00	4.50 2.90
Bacher et al. (1990) Canada	not reported	first or recurrent	71.00 (10.20)	39.58	ZSRD	subacute early subacute late chronic early chronic late	57.3 days 99.3 days 237.3 days 422.3 days	48 43 42 39	46.04 46.01 49.31 50.36	8.24 10.51 11.05 12.40
Barker-Collo et al. (2016) New Zealand [ARCOS-IV]	ischaemic	first or recurrent	70.89 (14.11)	47.00	HADS-D	subacute early subacute late chronic early	30 days 180 days 365 days	367 365 386	4.56 3.38 3.49	2.73 2.91 2.89
Brodaty et al. (2013) Australia [Sydney Stroke Study]	ischaemic	first or recurrent	72.13 (8.88)	42.11	GDS-15	subacute late chronic late chronic extended chronic extended	135 days 455 days 1,180 days 1,975 days	135 110 88 70	2.90 3.10 3.10 2.20	0.20 0.30 0.30 0.30
Clark & Smith (1998) Australia	not reported	first or recurrent	70.30 (10.60)	31.91	ZSRD	subacute early subacute early chronic early chronic late	18.4 days 58.1 days 238.2 days 423.1 days	94 94 94 94	47.80 46.10 48.90 47.80	10.60 8.80 11.50 11.30
Crowley & Andrews (2018) United Kingdom	ischaemic	first	65.68 (13.50)	34.15	HADS-D	subacute early chronic early	90 days 270 days	41 35	6.27 3.94	5.00 3.47
dosSantos et al. (2018) Brazil	mixed	first or recurrent	70.30 (7.60)	50.00	GDS-15	subacute early subacute late chronic early	20.6 days 96.6 days 200.6 days	50 50 50	3.90 3.50 2.90	3.60 3.50 2.70
Douven et al. (2018) Netherlands [CASPER]	mixed	first or recurrent	67.31 (11.80)	34.58	MADRS	subacute early chronic early chronic late	87 days 270 days 455 days	240 211 217	6.06 6.80 6.60	5.84 7.20 7.50
Eriksen et al. (2016) Norway [Post-Stroke Fatigue Study]	mixed	first	67.70 (13.00)	41.49	BDI	acute chronic early chronic late chronic late	7.5 days 187.5 days 372.5 days 552.5 days	94 94 94 94	9.60 9.70 8.90 9.70	7.50 7.40 6.30 7.20
Guo et al. (2017) Singapore	mixed	first	63.70 (10.10)	29.79	CESD-11	subacute early chronic early	90 days 365 days	94 78	18.70 18.47	6.84 6.82

Hadidi et al. (2011) United States	ischaemic	first	69.00 (11.90)	47.83	CESD-10	subacute early subacute early subacute early	14 days 30 days 90 days	23 23 23	4.40 3.90 2.80	4.00 2.70 2.30
Haley et al. (2011) United States [REGARDS]	mixed	first	71.27 (7.91)	50.74	CESD-4	chronic early chronic extended	275.46 days 1,506.86 days	133 133	0.95 1.88	1.82 2.89
Hamza et al. (2014) Nigeria	mixed	first	58.76 (13.24)	49.36	BDI	subacute late chronic early	180 days 365 days	233 217	12.30 10.30	5.0 4.0
Hjollund (2017) Denmark	mixed	first	not extrapolatable	36.40	HADS-D	subacute early subacute late chronic early chronic late chronic late chronic extended chronic extended chronic extended	90 days 180 days 365 days 545 days 730 days 910 days 1,095 days 1,275 days	101 818 846 806 820 789 519 223	3.90 4.40 4.70 4.60 4.50 4.40 4.60 4.50	3.60 3.90 3.90 3.80 3.80 3.80 4.20 3.90
Hu et al. (2020) China	mixed	first	not extrapolatable	29.23	PHQ-9	subacute early subacute early	30 days 90 days	65 65	3.25 2.66	3.11 2.57
Iacoboni et al. (1995) Italy	ischaemic	first	52.90 (8.80)	40.00	RDI	subacute early chronic late	15 days 380 days	20 20	47.66 44.90	14.59 12.35
Kruithof et al. (2015) Netherlands [FuPro-Stroke]	mixed	first	56.70 (10.80)	43.00	CESD-20	subacute early chronic early chronic extended	50.5 days 365 days 1,095 days	206 210 174	13.70 11.70 10.00	9.30 8.90 8.10
Ladwig & Werheid (2020) Germany	ischaemic	first or recurrent	63.60 (10.90)	40.26	GDS-15	subacute early chronic early chronic late	42 days 276 days 483 days	303 196 181	3.90 3.90 3.70	3.70 3.90 3.80
Landreville et al. (2009) Canada [ARMDA]	mixed	first or recurrent	76.91 (7.03)	48.73	GDS-30	subacute early subacute late chronic early	90.38 days 180.38 days 270.38 days	197 197 197	8.92 8.94 8.72	5.61 5.61 5.61
Lerdal & Gay (2013) Norway	mixed	first	67.80 (12.90)	40.63	BDI	acute chronic late	7 days 552 days	96 96	9.40 9.50	7.51 7.21
Liu et al. (2020) China	ischaemic	first	62.47 (10.45)	30.41	HADS-D	acute subacute early subacute late chronic early	7.54 days 37.54 days 97.54 days 187.54 days	217 215 208 209	4.76 6.37 5.92 6.03	3.80 5.24 5.96 5.93
Ormstad et al. (2012) Norway	ischaemic	first	67.70 (11.80)	40.00	BDI	subacute late chronic early chronic late	180 days 365 days 545 days	45 45 45	13.00 11.30 11.60	9.50 7.70 7.10
Pohjasvaara et al. (2001) Finland [Helsinki Stroke Aging Memory Study]	ischaemic	first or recurrent	69.90 (7.60)	46.85	BDI	subacute early chronic late	90 days 455 days	286 286	8.80 10.10	6.70 7.70

Robinson-Smith et al. (2000) United States	mixed	first or recurrent	71.00 range: 36, 92	44.44	CESD-20	subacute early subacute late	30 days 180 days	63 63	13.40 8.60	9.00 8.00
Schöttke et al. (2020) Germany	mixed	first or recurrent	67.51	50.00	CDS	subacute early chronic extended	45.71 days 1,170.60 days	56 31	4.59 10.85	5.12 8.23
Schultz et al. (1997) United States	not reported	first or recurrent	58.20	42.96	HDRS-17	subacute early subacute late chronic early chronic late	90 days 180 days 365 days 730 days	77 79 70 66	8.20 8.42 7.83 8.45	6.72 6.47 6.14 7.86
Sibon et al. (2012) France	mixed	first or recurrent	59.50 (12.80)	47.00	HDRS-17	acute subacute late	5.4 days 95.4 days	43 43	7.05 8.26	4.64 5.35
Teoh et al. (2009) Australia	mixed	first	67.50 (14.30)	31.85	CESD-20	chronic early chronic late chronic late	351 days 421 days 531 days	135 115 119	13.82 12.09 11.97	10.84 11.11 10.55
Townend et al. (2007) Australia	mixed	first or recurrent	75.60 (13.12)	52.00	HADS-D	acute subacute early subacute late	2.6 days 34 days 91 days	125 112 105	2.10 3.96 4.44	3.94 3.45 3.19
vanRijsbergen et al. (2020) Netherlands [COMPASS]	mixed	first or recurrent	64.00 (11.90)	30.32	HADS-D	subacute early chronic early	90 days 365 days	155 155	4.90 4.40	3.70 3.60
Volz et al. (2021) Germany [Berlin PSD Study]	ischaemic	first or recurrent	63.67 (10.81)	40.20	GDS-15	subacute early chronic early chronic late chronic extended chronic extended	51.3 days 300.6 days 531.2 days 829 days 1009 days	301 195 179 80 49	3.87 3.91 3.66 3.06 2.65	3.67 3.84 3.84 3.67 2.97
Yiu et al. (2012) Canada	mixed	first or recurrent	62.47 (10.13)	27.55	CESD-20	subacute late subacute late chronic early chronic late	96.9 days 156.2 days 246.2 days 431.2 days	98 86 81 72	15.29 12.59 12.77 11.25	9.11 8.61 9.96 7.61

Note. M = mean; *Mdn* = median; *SD* = standard deviation; IQR = interquartile range; EMMA = "Estudo de Mortalidade E Morbidade Do Acidente Vascular Cerebra" or the Study of Stroke Mortality and Morbidity; ARCOS-IV = Auckland Regional Community Stroke Study; CASPER = Cognition and Affect – a Prospective Evaluation of Risks study; REGARDS = Reasons for Geographic and Racial Differences in Stroke study; FuPro-Stroke = Functional Prognosis after stroke; ARMDA = Activity Restriction Model of Depressed Affect; COMPASS = Complaints After Stroke Study. CDS = Cornell Depression Scale (Alexopoulos et al., 1988); PHQ = Patient Health Questionnaire (Spitzer et al., 1994; Kroenke et al., 2001); ZSRD = Zung Self Rating Depression scale (Zung, 1965); HADS-D = Hospital Anxiety and Depression Scale – Depression subscale (Zigmond & Snaith, 1983); GDS = Geriatric Depression Scale (Yesavage et al., 1982); MADRS = Montgomery-Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979); BDI = Beck Depression Inventory (Beck, 1961); CESD = Center for Epidemiological Studies – Depression (Radloff, 1977); RDI = Rome Depression Inventory (Pancheri & Carilli, 1982); HDRS = Hamilton Depression Rating Scale (Hamilton, 1960).

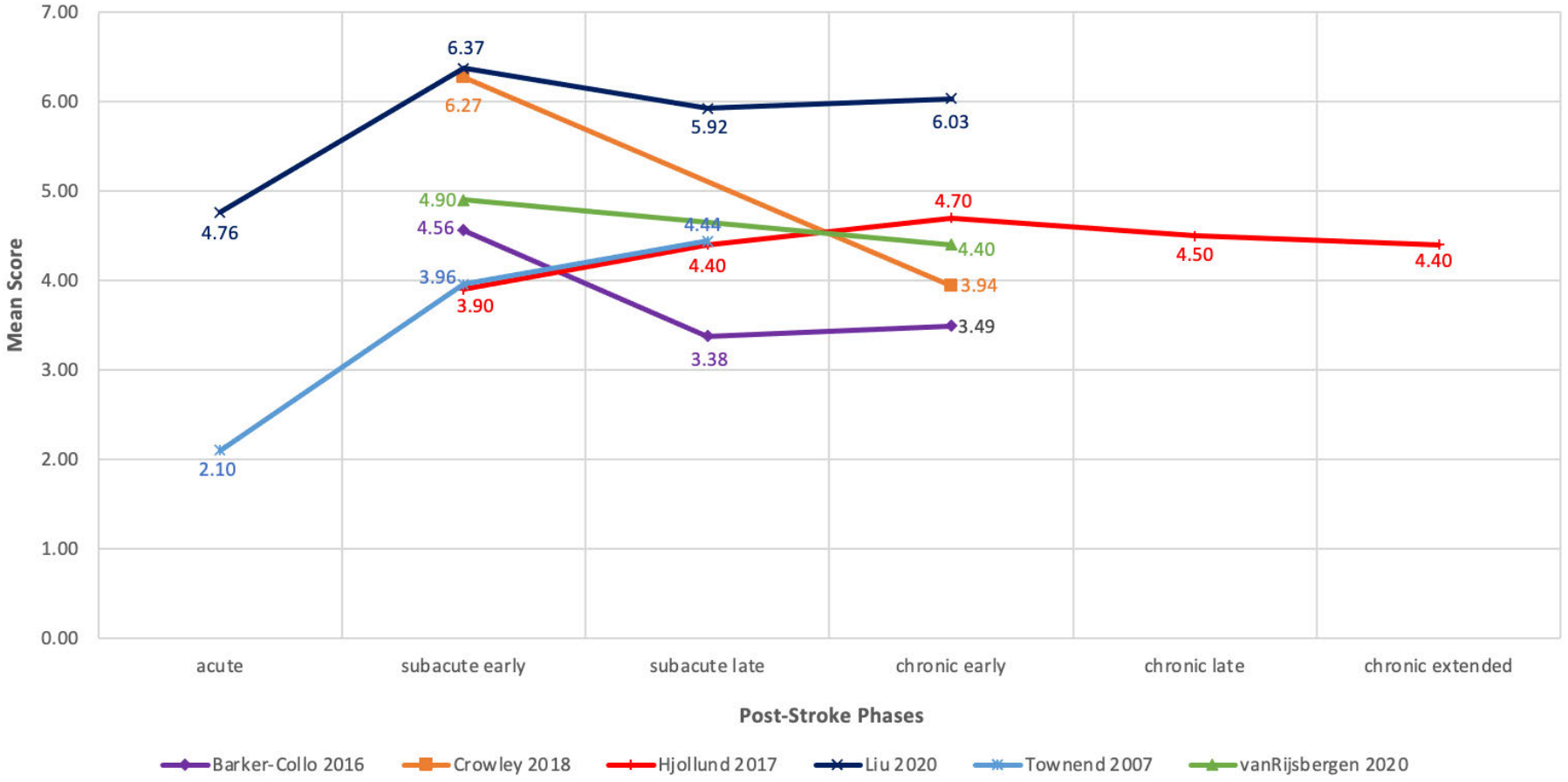
2.3.6 Frequencies and trajectories of depressive symptoms across post-stroke phases for studies that reported means (*n* = 33)

Mean Scores of Depressive Symptoms Utilising HADS-D (Figure 2.6)

Of the 10 measures used in the 33 studies that reported mean scores, the HADS-D was selected for analysis. The HADS-D was chosen because it was one of the most commonly used measures (6/33, 18.2%), and there was only one version in use. The mean scores of depressive symptoms reported by the six studies that utilised the HADS-D, mapped according to post-stroke phase, are presented in Figure 2.6. For studies that reported mean scores at multiple time points within any one of the post-stroke phases, the time point with the largest sample size was selected. The HADS-D subscale comprises seven items; each item is scored from 0 to 3, yielding an overall score ranging from 0 to 21 (Zigmond et al., 1983). Most of the assessment time points were concentrated in the subacute early, subacute late and chronic early phases. Across these three phases, the mean scores of most studies appeared to demonstrate relatively constant trajectories. The exception was one study that showed a decline in mean score from the subacute early phase to the chronic early phase (Crowley & Andrews, 2018). Two studies reported a mean score in the acute phase; both exhibited an increase in mean score at the subsequent phase and constant trajectories thereafter (Liu et al., 2020; Townend et al., 2007).

Figure 2.6

Mean Scores and Trajectories of Depressive Symptoms in Studies Utilising HADS-D, by Post-Stroke Phase



Note. HADS-D = Hospital Anxiety Depression Scale – depression subscale (Zigmond & Snaith, 1983). HADS-D score range: 0 to 21.
Post-stroke phases: acute ≤ 7 days; subacute early > 7 days to 3 months; subacute late > 3 months to 6 months; chronic early > 6 months to 12 months; chronic late > 12 months to 2 years; chronic extended > 2 years.

2.4 Discussion

From this review, it is difficult to draw conclusions about the trajectory of post-stroke depression because of the considerable heterogeneity of methodologies across the 63 included studies. First, there were differences in the type of outcome data pertaining to depression among the included studies. Most studies (n = 44) reported frequency, while other studies (n = 33) reported mean scores on measures of depressive symptoms. Some studies (n = 14) reported both types of outcome data. Acknowledging this difference, we adopted an approach that examined frequency outcomes separately from mean scores. Second, there was marked variation in the assessment time points used, across the included studies. Differences were observed in the time from stroke onset to the first assessment, the length of time between subsequent assessments, and the total duration of the study period. Recognising these large variations, we condensed the numerous time points into six post-stroke phases based on the SRRR framework (Bernhardt et al., 2017), to facilitate comparison of outcome data across time. Third, there was substantial variation in the methods by which depression was evaluated. There were 11 different measures utilised across the studies included in this review; 10 were screening measures for depressive symptoms and one was the DSM. Most measures had more than one version in use, and studies applied different cut-off scores. For example, six studies utilised the PHQ; four of these used the 9-item version and the other two used the 8-item version. Of the four studies that used the PHQ-9, different cut-off scores were applied (≥ 5 or ≥ 10). To address this variation we selected, for closer examination, subgroups of studies that utilised common and consistent measures, such as the DSM and the HADS-D. Hackett and Pickles (2014) and Ayerbe et al. (2013a) both described difficulties similar to those encountered by this review in relation to the heterogeneity of study methodology.

Following our approaches to address heterogeneity, it is possible to state some general findings about the trajectory of post-stroke depression. First, the prevalence of post-stroke depression varied across the studies that reported results by frequency. However, many studies reported a high prevalence, which was observed across each of the post-stroke phases. Second, depression appears to persist for years following stroke, with high prevalence observed even in the chronic extended phase (more than 2 years post-stroke). The high prevalence and long term persistence of post-stroke depression has previously been demonstrated by Ayerbe et al. (2013a) and Hackett and Pickles (2014); these authors reported a pooled point prevalence of 29 and 31 per cent respectively. In this review, of the 44 studies that reported frequency, 18 studies (18/44, 40.1%) observed a frequency of post-stroke depression of at least 30 per cent, at one or more assessment time points. Further, 28 studies (28/44, 63.6%) observed a frequency of post-stroke depression of at least 25 per cent, at one or more assessment time points.

Third, considerable disparity of the trajectories of post-stroke depression, as measured by frequency, was exhibited between cohorts, in both DSM (Figure 2.4) and HADS-D (Figure 2.5)

subgroup analyses. For both these subgroups, cohorts showed a variety of increasing, decreasing, variable or constant trajectories. In contrast, for the subgroup of studies that reported mean scores on the HADS-D, most demonstrated trajectories of scores that appeared to remain fairly constant, from the subacute early phase onwards (Figure 2.6). This observed difference between the trajectories of frequencies of depression as measured by HADS-D, and trajectories of mean HADS-D scores, likely reflects the characteristic of a cohort mean score that masks underlying variability in individual scores.

This review differs from those of Hackett and Pickles (2014) and Ayerbe et al. (2013a), in that studies required at least two assessment time points for inclusion. This criterion was applied because the focus of this review is on trajectory – the definition of which requires a minimum of two time points. Further, this current review differs in its definitions of post-stroke phases, which were based on phases described by the SRRR recovery framework (Bernhardt et al., 2017). Last, in order to explore the trajectory of post-stroke depression using an alternative approach, this review also included studies that reported outcome data as continuous variables with mean scores. These data were analysed separately from the analysis of frequencies of the presence of depression or depressive symptoms.

In future research, we recommend that trajectories of the status of post-stroke depression experienced by individuals, within a study cohort, are explored over time. These studies should include multiple assessment time points, with at least one assessment within each of the phases suggested by this review, and with a study duration of at least one year post-stroke. The experience gained from this review also suggests that future longitudinal studies of post-stroke depression should carefully define assessment time points. Clearly defined time points, quantifiable by a unit of time following stroke onset, are essential to enable the comparison of results across studies. The additional recording of clinical events may also be useful, because events such as discharge from hospital to home may influence a change in depressive symptoms – such as the onset or resolution of depression.

2.5 Conclusion

The heterogeneity across the studies included in this review impacts the ability to draw definitive conclusions about the trajectory of post-stroke depression. Nonetheless, this review confirms that post-stroke depression is prevalent and persists into chronic phases. This review has shown that currently there is insufficient evidence to suggest a single ‘typical’ trajectory of post-stroke depression in cohorts of stroke survivors. However, it may be that there are varying and dynamic trajectories exhibited by individual stroke survivors. Characterising depression in individual stroke survivors, over time, is important in order to provide further insight into trajectories of post-stroke depression.

Chapter 3.

Common Methodology

The common methodology for the empirical research studies presented in this thesis, in Chapters 5, 7 and 8, is described in this chapter. There are three sections to this chapter, as follows:

- 3.1 Study Design
- 3.2 Study Measures
- 3.3 Statistical Methods and Analyses
- 3.4 Glossary of Statistical Terminology

3.1 Study Design

The empirical research studies included in this thesis (Chapters 5, 7 and 8) are prospective, observational and longitudinal in design. Each of these studies utilises demographic and clinical data from the Stroke Imaging Prevention and Treatment (START) collaborative research program. This was a multicentre, Australasian cohort study of adult ischaemic stroke survivors with recruitment between June 2010 and April 2013.

3.1.1 START collaborative research program

The Stroke Imaging Prevention and Treatment (START) collaborative research program comprised two arms:

- Prediction and Prevention to Achieve optimal Recovery Endpoints after stroke (START PrePARE) (Carey et al., 2015)
- Extending the Time for Thrombolysis in Emergency Neurological Deficits (START EXTEND) (Ma et al., 2012)

START PrePARE

The START PrePARE arm was a longitudinal, observational, cohort study that examined clinical outcomes in adult ischaemic stroke survivors (National Trials Australia 0902). Participants were recruited within 3 days post-stroke and were followed up over the 12 month study period. A proportion of START PrePARE participants were also enrolled in the START EXTEND arm, if eligible (Carey et al., 2015).

START EXTEND

The START EXTEND arm was a randomised, double-blinded, placebo-controlled phase III clinical trial (National Trials Australia 0901). The trial examined the use of thrombolysis with tissue plasminogen activator (tPA) in adults with acute, ischaemic stroke. Participants were

enrolled in the START EXTEND arm between 4.5 and 9 hours following stroke onset, if they met additional inclusion criteria associated with suitability for thrombolysis (Ma et al., 2012). The START EXTEND arm comprised:

- a clinical trial for participants who were randomised to receive either tPA or placebo, and
- a cohort study for participants who did not achieve ischaemic penumbral criteria for randomisation, but who were monitored via this cohort study

3.1.2 Eligibility

Inclusion criteria for enrolment in both START PrePARE and START EXTEND study arms required participants:

- to be clinically diagnosed with acute ischaemic stroke, confirmed by Magnetic Resonance Imaging (MRI)
- to be at least 18 years of age
- to be English-speaking
- to have no significant disability prior to stroke onset, as determined by an estimated modified Rankin Scale (mRS) (Bonita & Beaglehole, 1988) score ≤ 2

Exclusion criteria for enrolment in both study arms were:

- a terminal illness from which the patient would not be expected to survive more than 12 months
- a current pregnancy
- any contraindication to imaging with MRI, such as the presence of a pacemaker, a cerebral aneurysm clip, an implanted insulin pump or metal within the orbit of the eye

There were additional inclusion criteria required for suitability for thrombolysis, for enrolment in the START EXTEND study arm, including a score within the range 4 to 26 inclusive, on the National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989). Detailed eligibility criteria for participation in both START PrePARE and START EXTEND study arms are described in Appendix D.

3.1.3 Consent and ethics

Written, informed consent by the participant or their legally responsible person was required for participation, prior to enrolment in either study arm. The START collaborative research program was approved by ethics committees at each recruiting hospital and associated tertiary institutions (Appendix E).

3.1.4 Recruitment

Participants who met eligibility criteria for the START collaborative research program were recruited consecutively between June 2010 and April 2013. Following recruitment, all participants were reassessed at subsequent time points, unless they were unavailable or had chosen to withdraw. The planned sample size was 200 participants at the 3 month time point post-stroke; replacement participants were recruited to meet this target.

Hospital recruitment sites

Participants were recruited from 19 hospitals throughout Australia and New Zealand, all of which had specialised stroke units. The hospital recruitment sites, categorised by state or country, are listed below:

- Victoria: Royal Melbourne Hospital, Western Hospital, Austin Hospital, Monash Medical Centre, Box Hill Hospital, Epworth Hospital Richmond
- New South Wales: John Hunter Hospital, Westmead Hospital, Royal North Shore Hospital, Gosford Hospital, St Vincent's Hospital
- South Australia: Royal Adelaide Hospital, Flinders Medical Centre, Lyell McEwin Hospital, The Queen Elizabeth Hospital
- Queensland: Nambour General Hospital, Royal Brisbane and Women's Hospital
- Western Australia: Sir Charles Gairdner Hospital
- New Zealand: Auckland City Hospital

3.1.5 Study procedure

The START research program encompassed the collection of a profile of outcome measures, including blood based markers, neuroimaging and clinical data. Standardised assessments were undertaken by health professionals, trained in the conduct of the measures, at hospital recruitment sites or participants' homes. All participants were assessed at admission, at baseline and at subsequent time points during the first 12 months following stroke onset. The writer did not have a role in the START research program design, recruitment or data collection.

Assessment time points

The assessment time points selected for the START research program were:

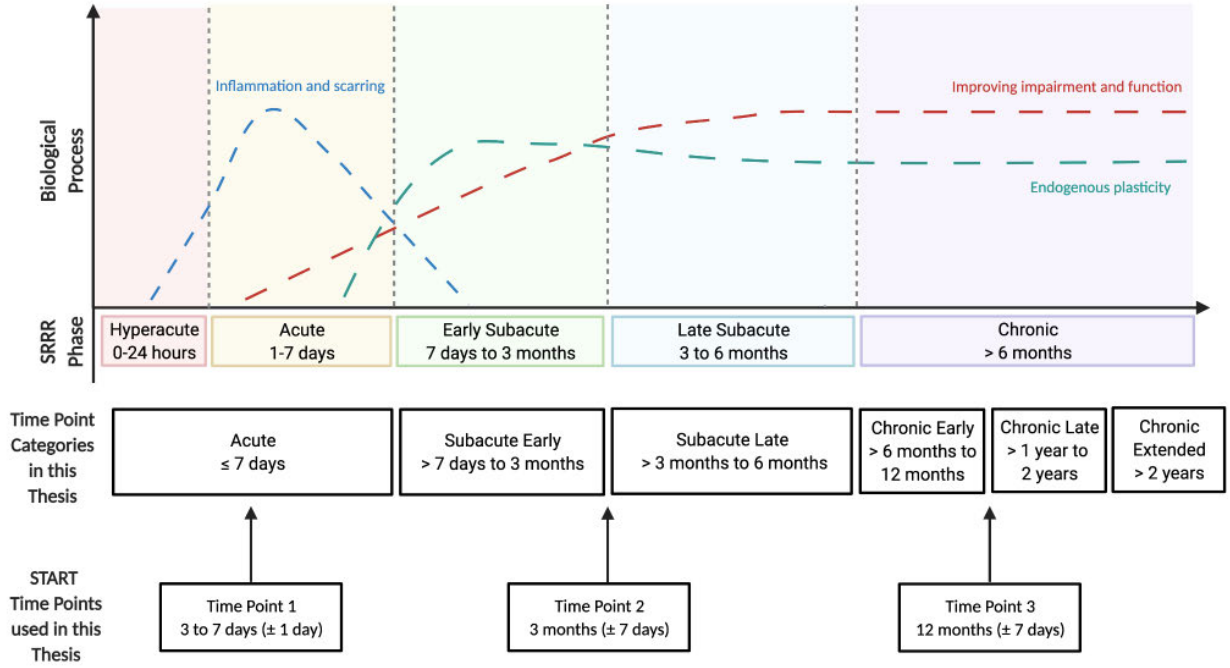
- on admission
- at baseline (within 12 to 24 hours of stroke onset)
- within the first week (3 to 7 days, ±1 day, from stroke onset)
- at 3 months (±7 days) from stroke onset
- at 12 months (±7 days) from stroke onset

Stroke survivors were enrolled into the START EXTEND study arm on admission, usually within nine hours post-stroke, and were assessed on admission, at baseline and at the subsequent time points. For the START PrePARE study arm, stroke survivors could be enrolled on admission, at baseline or up until three days post-stroke; these participants were assessed on enrolment and at the subsequent time points.

In this thesis, the empirical research studies focus on outcome data collected within the first week (3 to 7 days, ±1 day), at 3 months (±7 days) and at 12 months (±7 days) following stroke onset. These time points align with key post-stroke phases described in a recovery framework developed by the Stroke Recovery and Rehabilitation Roundtable (SRRR); this framework is underpinned by knowledge of the biology of stroke recovery (Bernhardt et al., 2017). The 'first week' time point corresponds with the 'acute' phase (1 to 7 days post-stroke). The '3 month' time point corresponds with the intersection of the 'early subacute' (7 days to 3 months post-stroke) and 'late subacute' (3 to 6 months post-stroke) phases. The '12 month' time point correlates with the 'chronic' phase (more than 6 months post-stroke) (Figure 3.1).

Figure 3.1

Assessment Time Points and Key Post-Stroke Phases



Note. This figure has been adapted from Figure 1 in Bernhardt et al. (2017), which depicts post-stroke phases that link to the currently known biology of recovery, developed by the Stroke Recovery and Rehabilitation Roundtable. Figure included with permission from SAGE publishing.

Data storage

Data obtained from each assessment, for each participant at each time point, were deidentified and entered into an electronic Case Report Form (eCRF) attached to the study database. Access to the study database was secured by password protection. The original data were recorded on paper; these documents were stored securely at each hospital recruitment site and will be destroyed after 15 years.

Data quality checking

During the development of this thesis, the dataset was checked for quality. Entries identified as possibly being inconsistent or erroneous were discussed with the lead researcher, the data custodian and the research team. The rationale for any amendments made to the dataset was documented.

3.2 Study Measures

A suite of standardised clinical assessments was undertaken over the course of the first year following stroke onset. The measures were administered by the research coordinator or research assistants, all of whom were healthcare professionals trained in the conduct of each assessment using standard procedures. Outcome measures are used in stroke research and clinical practice to quantify recovery, monitor progress and plan rehabilitation (Duncan, 2013a). These measures are often administered at baseline, and at subsequent time points, to assess change and to inform clinical decision-making (Li et al., 2020). The utility and psychometric properties of each measure selected for inclusion in the START research program were considered. Each measure was deemed fit-for-purpose in its use in the research program (Carey et al., 2015; Ma et al., 2012). In this thesis, the empirical research studies utilised data from stroke-specific measures and from other assessments not specific to stroke, but which are widely used in stroke research and practice.

Inclusivity

During the recruitment phase, all stroke survivors who met the predetermined eligibility criteria were invited to participate in the study, including individuals with communication deficits or cognitive impairments. To facilitate inclusivity, the START research team developed an aphasia-friendly protocol (Brennan et al., 2005; Carey et al., 2015), in consultation with a speech pathologist with expertise in stroke and aphasia. Accordingly, non-verbal supports and other strategies were used in the administration of measures for participants with aphasia, dysphasia or cognitive impairment (Brennan et al., 2005). For example, response cards were devised that demonstrated both a large print text answer (such as ‘not difficult at all’) and a corresponding numerical value (such as ‘5’). Following the participant’s indication of their answer using the

response cards, the examiner confirmed the answer by restating the corresponding text and numerical responses.

Proxy reporting

The use of proxy reporting was supported if a participant was unable to respond directly to the modified Rankin Scale (mRS), Barthel Index (BI) or Stroke Impact Scale (SIS). Demographic data and questions related to prior history of depression, comorbid conditions and medications could also be collected from a proxy if the patient was unable to provide this information. A proxy was defined as someone who knew the patient well and was familiar with their daily routine and circumstances, such as a spouse or close relative.

Demographic and clinical characteristics

A standardised set of questions was developed to collect demographic and clinical information from each participant at enrolment into the study. Demographic information included: age at stroke onset, sex, hospital recruitment site, ethnicity, highest level of education completed, employment type, living arrangement and relationship status. Clinical characteristics included: pre-stroke level of disability (mRS); previous history of stroke; stroke-related neurological severity (NIHSS); history of pre-stroke depression; and other comorbid conditions.

3.2.1 Overview of Measures

In this thesis, the empirical research studies (Chapters 5, 7 and 8) utilise the following measures:

- Modified Rankin Scale (mRS) (Bonita & Beaglehole, 1988)
- Patient Health Questionnaire, 2-item (PHQ-2) (Kroenke et al., 2003)
- Charlson Comorbidity Index (CCI) (Charlson et al., 1987)
- National Institute of Health Stroke Scale (NIHSS) (Brott et al., 1989)
- Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979)
- Stroke Impact Scale (SIS) (Duncan et al., 2003a)
- Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002)
- Barthel Index (BI) (Mahoney & Barthel, 1965)

A complete version of each measure is included in the appendices (Appendix F to Appendix Q). Table 3.1 provides a brief description of the purpose of each measure, the score range, and the empirical research study or studies in which each measure is used.

Table 3.1

Overview of Assessments

Measure	Abbreviation	Purpose of the measure	Score range	Empirical research study
modified Rankin Scale	mRS	disability and dependence	0-6	1, 2, 3
Patient Health Questionnaire	PHQ-2	depressive symptoms	0-6	1, 2
Charlson Comorbidity Index	CCI	comorbidity burden	0-35	3
National Institutes of Health Stroke Scale	NIHSS	neurological severity	0-42	1, 2, 3
Montgomery-Åsberg Depression Rating Scale	MADRS	depressive symptoms	0-60	1, 2
Stroke Impact Scale [a]	SIS			
Stroke Impact Scale Index	SIS Index	overall stroke impact	20-100	2, 3
Stroke Impact Scale 16	SIS-16	impact on physical function	16-80	2
Stroke Impact Scale Visual Analogue Scale	SIS VAS	overall recovery	0-100	2, 3
Work and Social Adjustment Scale	WSAS	impact on work and social roles	0-40	2
Barthel Index	BI	independence with ADL	0-100	2

Note. ADL = Activities of Daily Living

[a] Variants of the Stroke Impact Scale used in the empirical research studies presented in this thesis.

Schedule of study assessments

In this thesis, the empirical research studies (Chapters 5, 7 and 8) utilised data from measures undertaken at baseline (12 to 24 hours), within the first week (3 to 7 days, ± 1 day), at 3 months (± 7 days) and at 12 months (± 7 days) following stroke onset. The schedule of study assessments used in research in this thesis is presented in Table 3.2.

Table 3.2

Schedule of Study Assessments Used in Research Reported in this Thesis

At baseline (12-24 hours)	Within the first week (day 3 to 7, ± 1 days)	At 3 months (± 7 days)	At 12 months (± 7 days)
modified Rankin Scale (mRS) [a]	–	–	–
Patient Health Questionnaire-2 (PHQ-2) [b]	–	–	–
Charlson Comorbidity Index (CCI)	–	–	–
–	National Institute of Health Stroke Scale (NIHSS)	–	–
–	Montgomery-Åsberg Depression Rating Scale (MADRS)	Montgomery-Åsberg Depression Rating Scale (MADRS)	Montgomery-Åsberg Depression Rating Scale (MADRS)
–	–	Stroke Impact Scale (SIS)	Stroke Impact Scale (SIS)
–	–	Work and Social Adjustment Scale (WSAS)	Work and Social Adjustment Scale (WSAS)
–	–	Barthel Index (BI)	Barthel Index (BI)

Note. [a] Estimated pre-stroke disability was measured by the modified Rankin Scale (mRS) at baseline. [b] Prior history of depression was measured by the Patient Health Questionnaire 2 (PHQ-2) at baseline.

3.2.2 Modified Rankin Scale (mRS)

The modified Rankin Scale (mRS) is a stroke-specific scale that measures degree of disability and dependence (Bonita & Beaglehole, 1988). The mRS categorises stroke patients into one of seven discrete, ordinal grades that describe the full range of functional outcomes. Stroke survivors are assigned a score ranging from 0 (denoting no disability and functional independence), to a score of 5 (representing severe disability and complete dependence – that is, bed-ridden, incontinent and requiring constant care). The highest possible score is 6, recorded for deceased patients (Bonita & Beaglehole, 1988). The mRS is a widely used outcome measure in stroke research and clinical practice (Banks & Marotta, 2007).

The mRS is a modified version of the Rankin Scale (Rankin, 1957); the original version was developed to provide descriptive categories of functional recovery for cerebrovascular disease in patients 60 years and older (Banks & Marotta, 2007). In the original Rankin Scale, patients were classified into one of five grades; the modified version includes two additional grades (0 and 6) which extend the original five (1 to 5) (Rankin, 1957). The mRS is presented in Appendix F.

In the START research program, the mRS was administered at enrolment to retrospectively determine pre-stroke level of disability, as per eligibility criteria. Inclusion criteria required participants to have no significant disability before the index stroke, as estimated by an mRS score ≤ 2. In this thesis, estimated pre-stroke mRS scores were used to characterise the sample in each empirical research study (Chapters 5, 7 and 8).

3.2.3 Patient Health Questionnaire 2 (PHQ-2)

Previous history of depression was obtained from medical history and participant interview, using a set of structured interview questions at baseline. These questions had been developed from the Composite International Diagnostic Interview (CIDI) (Kessler & Ustün, 2004) in consultation with a neuropsychiatry specialist. Subsequently, participants' responses to these questions were transformed into scores on the Patient Health Questionnaire 2-item version (PHQ-2) (Spitzer et al., 1994; Kroenke et al., 2003). The PHQ-2 is an abbreviated version of the original 9-item version (Kroenke et al., 2001); the PHQ-9 was derived from the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (Spitzer et al., 1994).

The PHQ-2 comprises the first two items of the PHQ-9, and reflect the core symptoms of major depression: low mood and anhedonia (loss of interest or pleasure in activities previously enjoyed). For both items, the stem question is: "Over the last two weeks, how often have you been bothered by any of the following problems?" and the two items are: "little interest or pleasure in doing things" (anhedonia) and "feeling down, depressed or hopeless" (low mood). Each item is rated on a 4-point Likert scale, with the response options: "not at all", "several days", "more than half the days" and "nearly every day", scored as 0, 1, 2 and 3 respectively (Kroenke et al., 2003). The scores assigned for each item are added to provide an overall score, which ranges from 0 to 6. A PHQ-2 score ≥ 3 is considered to be the optimal cut-off for the purpose of screening for depression (Staples et al., 2019). The PHQ-2 is presented in Appendix G.

3.2.4 Charlson Comorbidity Index (CCI)

The Charlson Comorbidity Index (CCI) measures comorbidity burden (Charlson et al., 1987). A comorbidity is a medical condition that co-exists, in an individual, with the condition of interest – in this case, ischaemic stroke. The CCI was originally developed using hospital discharge International Classification of Disease revision 9 (ICD-9) codes to predict mortality (Bar & Hemphill, 2011). The index has been validated to predict functional outcomes within the stroke population (Tessier et al., 2008).

The CCI was used in the START research program to measure comorbidity at the time of stroke onset. Scores were calculated retrospectively from patient or proxy interviews and medical records, at baseline. The index was scored by assigning a value of 1, 2, 3, or 6 to each medical condition that antedated the stroke, based on its one year mortality risk (Charlson et al., 1987).

The following medical conditions were assigned a score of 1: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, ulcer disease, mild liver disease and diabetes. These conditions were assigned a score of 2: diabetes with end organ damage, any tumour, leukemia and lymphoma. Moderate or severe liver disease was scored 3; metastatic solid tumour and Acquired Immune Deficiency Syndrome (AIDS) were scored 6. The scores for each existing condition were summated to yield a total score for each participant, reflecting their cumulative burden of comorbidities – with higher scores indicating greater comorbidity burden (Fischer et al., 2006). In the START research program, all participants received a score of at least 1 on the CCI, reflecting the presence of cerebrovascular disease as a consequence of the index stroke. The CCI was used in Empirical Research Study 3 (Chapter 8) as a continuous independent variable. The CCI is presented in Appendix H.

3.2.5 National Institutes of Health Stroke Scale (NIHSS)

The National Institutes of Health Stroke Scale (NIHSS) is used to measure stroke-related neurological deficit (Brott et al., 1989). The scale was originally designed to measure baseline neurological status in acute stroke clinical trials; it is now widely used as an assessment to evaluate acuity of stroke patients, to determine appropriate treatment and to predict outcomes (Young et al., 2005). The NIHSS is a 15-item scale comprising 11 domains. Item 1 Level of Consciousness comprises three sub-items (1a, 1b and 1c). Item 5 Motor Arm and Item 6 Motor Leg each comprise two sub-items (5a, 5b; 6a, 6b). The remaining eight domains have one item each. Each item is scored on an ordinal scale with 3, 4 or 5 grades, ranging from 0 to 2, 0 to 3, or 0 to 4 (Kwah & Diong, 2013). For each item, a score of 0 is assigned if the patient presents with no deficit relative to that impairment or item. Scores on each of the 15 items, including sub-items, are added to yield an overall score, ranging from 0 (reflecting no neurological deficit) to 42 (indicating severe deficit) (Schlegel et al., 2003). Scores on the NIHSS can be categorised for interpretation in several ways. In the empirical research studies (Chapters 5, 7 and 8), NIHSS scores are stratified as follows: scores from 0 to 6 indicate mild neurological symptoms; scores from 7 to 16 indicate moderate neurological impairment; and scores ≥ 17 denote severe neurological impairment (Rost et al., 2016). The NIHSS is presented in Appendix I.

3.2.6 Montgomery-Åsberg Depression Rating Scale (MADRS)

The Montgomery-Åsberg Depression Rating Scale (MADRS) is used to assess for the presence and severity of depressive symptoms (Montgomery & Åsberg, 1979). It was selected for use in the START research program because the MADRS has been shown to be more accurate than other measures that also screen for post-stroke depression (Kang et al., 2013). The MADRS items focus on core mood symptoms, whereas other measures also assess for motor retardation and somatic symptoms. The MADRS comprises ten items: apparent sadness, reported sadness, inner

tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal ideation. Each item is scored on a 7-point Likert scale from 0 to 6. The maximum possible total score is 60, with higher scores indicating more severe depressive symptoms (Montgomery & Åsberg, 1979).

In the START research program, the Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA) was utilised in the administration of the MADRS (Williams & Kobak, 2008). This guide asks the respondent about their mental state over the preceding one week. Structured interview guides are increasingly used in the deployment of rating scales as they enable interviewers to score items more precisely. The MADRS SIGMA has been shown to yield high inter-rater reliability (intraclass correlation coefficient of 0.93) (Williams & Kobak, 2008), which was particularly important in the START research program to standardise its use across multiple assessors, at multiple locations. In addition, a training video was produced by the START research team, in consultation with medical specialists, to facilitate standardised administration of the measure.

In two of the empirical research studies presented in this thesis, MADRS scores are used as either a categorical, binary variable (Empirical Research Study 1) or as a continuous variable (Empirical Research Study 2). When used as a categorical variable, MADRS scores were dichotomised to depressive symptoms 'present' (score ≥ 7) or 'absent' (score < 7). The MADRS is presented in Appendix J and the MADRS SIGMA is presented Appendix K.

3.2.7 Stroke Impact Scale (SIS)

The Stroke Impact Scale (SIS) version 3.0 is a patient-reported outcome measure that captures the impact of stroke across multiple domains (Duncan et al., 2003a). The SIS comprises 59 items across eight domains: strength (4 items), hand function (5 items), activities of daily living (10 items), mobility (9 items), communication (7 items), emotion (9 items), memory and thinking (7 items) and social participation (8 items). Each item asks the participant to score their ability regarding a specific activity, over the previous two weeks. Responses are scored on a 5-point Likert scale from 1 ("could not do at all") to 5 ("not difficult at all"). Three items in the emotion domain (3f, 3h and 3i) change polarity; that is, when manually scored these items require reverse scoring. Each of the eight domain scores remain separate and are not aggregated into an overall score (Duncan et al., 2003a). The SIS is presented in Appendix L.

In Empirical Research Studies 2 and 3 (Chapters 7 and 8), three established variants of the SIS were used, each of which have been designed to yield a single overall score. These variants are the SIS Index (Jenkinson et al., 2013), the SIS-16 (Duncan et al., 2003b) and the SIS Visual Analogue Scale (VAS) (Duncan et al. 2003a).

SIS Index

The SIS Index measures patient perception of the overall impact of stroke. It was derived to yield a single index score and has been validated in a cohort of stroke patients (Jenkinson et al., 2013). The index score is generated by aggregating all SIS domain scores and standardising this on a scale from 20 to 100. The formula for this standardisation is presented in Figure 3.2. Higher scores indicate lesser impact of stroke, as perceived by the patient (Jenkinson et al., 2013). The SIS Index was used in Empirical Research Studies 2 and 3 (Chapters 7 and 8) as a continuous outcome variable.

Figure 3.2

Formula for the SIS Index Score

```
SIS Index Score = [actual raw score x 100] / [possible raw score]
```

SIS-16

The SIS-16 measures patient perception of the impact of stroke specifically on physical function Duncan et al., 2003b). The SIS-16 was developed as an abridged version of the SIS by using items only from the four physical function domains. Initially, this comprised 28 items; however, the minimal subset of these items that met adequate reliability and concurrent validity with the Barthel Index (BI) was calculated in order to yield a composite physical function measure. Subsequently, the final version of the SIS-16 comprised 16 items across three domains: hand function (1 item), mobility (8 items) and activities of daily living (7 items). The 16 item scores across these three domains are added and standardised to a scale from 20 to 100, using the same formula as the SIS Index (Figure 3.2). Higher scores on the SIS-16 correspond to lesser impact of stroke on physical functioning, as perceived by the patient (Duncan et al., 2003b). The SIS-16 was used in Empirical Research Study 2 (Chapter 7) as a continuous outcome variable. The SIS-16 is presented in Appendix M. The items of the SIS-16, with their corresponding item and domain score in the full version of the SIS 3.0, are presented in Appendix N.

SIS Visual Analogue Scale (SIS VAS)

The SIS VAS measures patient perception of overall recovery after stroke. It is a single question on the SIS, independent of the eight domains, that asks the respondent to rate their overall recovery following stroke, on a vertical visual analogue scale from 0 (“no recovery”) to 100 (“full recovery”) (Duncan et al., 2003b). The SIS VAS is presented in Appendix O. The SIS VAS was used in Empirical Research Studies 2 and 3 (Chapters 7 and 8) as a continuous outcome variable.

3.2.8 Work and Social Adjustment Scale (WSAS)

The Work and Social Adjustment Scale (WSAS) measures participation and functioning in work and social activities (Mundt et al., 2002). The WSAS asks the respondent to estimate how much their work and social roles and activities have been impacted by the particular health problem, across five domains: work duties, home management, social leisure, private leisure and close relationships. There is one question for each domain; responses are rated on a 9-point Likert scale from 0 ("no impairment") to 8 ("very severely impaired") (Jones et al., 2020). Scores obtained from each item are summed to yield a total score, ranging from 0 to 40 (Mundt et al., 2002) – with higher scores indicating greater impairments when returning to previous activities and roles (Thandi et al., 2017).

The original version of the WSAS was developed to evaluate the impact on function in individuals who experienced phobias; this version comprised four domains: work, home, social and personal leisure (Marks, 1986). The WSAS was adapted with the addition of a fifth domain pertaining to interpersonal relationships (Thandi et al., 2017). The WSAS has been used across cohorts with a range of health conditions, including stroke cohorts (Tse et al., 2017b; Hommel et al., 2009). The WSAS is presented in Appendix P. In Empirical Research Study 2, the WSAS was used a continuous outcome variable.

3.2.9 Barthel Index (BI)

The Barthel Index (BI) evaluates functional independence in activities of daily living and mobility (Mahoney & Barthel 1965). The BI was originally designed to assess independence of patients with neuromuscular or musculoskeletal disorders (Mahoney & Barthel, 1965); it is now well-established and widely used in stroke rehabilitation and research (Quinn et al., 2009; Ohura et al., 2017). The BI comprises 10 items, each scored in increments of five points. Two items (bathing and personal hygiene) are rated on a 2-point scale (0 or 5); six items (feeding, dressing, bowel management, bladder management, accessing the toilet, and ascending or descending stairs) are scored on a 3-point scale (0, 5 or 10); and the last two items (transferring and mobility) are scored on a 4-point scale (0, 5, 10 or 15) (Mahoney & Barthel, 1965). For each item, a minimum score of 0 denotes inability to perform the activity independently, and the maximum score (5, 10 or 15 depending on the item) represents complete independence in that activity. Domain scores are added to generate an overall score, which ranges from 0 (indicating complete functional dependence) to 100 (representing complete independence in activities of daily living) (Wallace et al., 2002; Uyttenboogart et al., 2007). The BI is a 20-point ordinal scale, transformed to scores on a scale from 0 to 100, in increments of five. Each item is scored by observation from the assessor or clinician and is based on whether the participant can undertake or perform the activity independently (Castiglia et al., 2017). The BI is presented in Appendix Q. In Empirical Research Study 2, the BI was used as a continuous outcome variable.

3.3 Statistical Methods and Analyses

The empirical research studies presented in this thesis (Chapters 5, 7 and 8) utilise both descriptive and inferential statistics. All analyses were conducted using the statistical software package Stata, versions 14 and 16 (StataCorp 2015; StataCorp, 2019). The Stata codes used to conduct the main analyses in the empirical research studies are included in Appendix R.

3.3.1 Descriptive statistics

Descriptive statistics were used to summarise demographic and clinical characteristics of the START cohort, and of the samples used in the empirical research studies (Chapters 5, 7 and 8). For categorical data, frequencies (*n*) and percentages (%) were reported. For continuous variables, measures of central tendency and dispersion were reported, according to the normality or skewness of the data. For normal distributions, means (*M*) and standard deviations (*SD*) were reported; for skewed distributions, medians (*Mdn*) and interquartile ranges (IQR: Q1, Q3) were presented.

3.3.2 Inferential statistics: regression analyses

The main inferential statistical methods utilised in this thesis were:

- logistic regression (Empirical Research Study 1);
- random effects logistic regression (Empirical Research Study 1); and
- quantile regression (Empirical Research Studies 2 and 3).

Logistic regression

In Empirical Research Study 1, logistic regression modelling was used to investigate whether participants with depressive symptoms at earlier time points were more likely, or less likely, to experience depressive symptoms at later time points – compared to those without such symptoms. The presence of depressive symptoms at earlier time points was the independent variable and their presence at later time points was the dependent variable. Models were applied for three time point dyads: first week versus 3 months; first week versus 12 months; and 3 months versus 12 months. For each time point dyad, odds ratio (*OR*), corresponding 95 per cent confidence interval (95% CI) and *p* values were reported.

Random effects logistic regression

In Empirical Research Study 1, random effects models were used in logistic regression to investigate the association between time post-stroke (independent variable) and the presence of depressive symptoms (dependent variable). Individual participants were used as random effects in this model. For each time point dyad (3 months versus first week and 12 months versus first week), the odds ratio (*OR*), the corresponding 95 per cent confidence interval (95% CI) and the *p* value were reported.

Quantile regression

In Empirical Research Studies 2 and 3, it was observed that most participants recorded high scores on the outcome measures used in each analysis; this raised the question of presence of heteroscedasticity in the data. Accordingly, Breusch-Pagan tests were conducted, yielding *p* values predominantly less than 0.05 (Breusch & Pagan, 1979), which confirmed the presence of heteroscedasticity in the data and supported the use of quantile regression. In Empirical Research Study 2, quantile regression was used to explore the association between depressive symptoms and recovery outcomes. Similarly, in Empirical Research Study 3, quantile regression was employed to explore the association between comorbidity burden and recovery outcomes. Each quantile regression model was fitted at the .25, median and .75 quantiles, at both 3 and 12 months. The influence of covariates (age, sex and neurological stroke severity) was controlled in each model. For each analysis, a coefficient and a *p* value were reported.

3.3.3 Other statistical methods utilised

Other statistical methods were utilised in the empirical research studies to address commonly occurring issues that arose. These issues and methods are described in the following paragraphs.

Comparing characteristics of included and non-included participants

Characteristics of included and non-included participants were compared in all empirical research studies. For continuous variables (for example, age at stroke onset and neurological stroke severity), Mann-Whitney U tests were conducted. For categorical variables (for example, sex and pre-stroke disability), Pearson's Chi-square tests were undertaken. For both tests, a statistically significant difference was observed if $p \leq 0.05$.

Controlling for covariates

In Empirical Research Studies 2 and 3, three covariates associated with post-stroke recovery were controlled in each quantile regression model. The covariates were: age at stroke onset (Knoflach et al., 2012), sex of the stroke survivor (Bushnell et al., 2014) and neurological stroke severity (Rost et al., 2016).

Estimating multicollinearity

In Empirical Research Studies 2 and 3, an auxiliary regression was conducted for each independent variable on the other independent variables, in order to estimate the presence of multicollinearity. Variance Inflation Factors (VIF) and Condition Numbers (CN) were calculated to determine the degree of multicollinearity. It was expected that some multicollinearity would be detected because age and stroke severity have been shown to be correlated.

Adjusting for multiplicity

In Empirical Research Studies 2 and 3, the significance level was corrected for multiplicity using the Bonferroni method. Accordingly, the level of statistical significance was set at $p \leq 0.005$ in Empirical Research Study 2 and $p \leq 0.025$ in Empirical Research Study 3.

3.4 Glossary of Statistical Terminology

The purpose of this glossary is to briefly define statistical concepts and terminology used in this thesis, with reference to the specific empirical research studies in which the concept arises (Table 3.3). Terms that appear in boldface within the definitions are also defined in this glossary.

Table 3.3

Glossary of Statistical Terminology Relevant to this Thesis

Terminology	Definition and brief explanation relevant to this thesis
Bonferroni method; Bonferroni correction	A method for adjusting the **significance level** when multiple statistical tests are performed simultaneously on the same sample. The formula for Bonferroni correction is: $\alpha = 0.05/n$ In this formula, α is the adjusted significance level, 0.05 is the conventional significance level and *n* denotes the number of tests. This is undertaken to counteract the problem of **multiplicity** and to protect against type 1 error inflation, which is the rejection of a true null hypothesis (Armstrong, 2014). The Bonferroni correction was applied to the significance level in Empirical Research Studies 2 and 3; the significance level was set at 0.005 and 0.025, respectively.
Breusch-Pagan test	A test to estimate the presence of **heteroscedasticity** in a **regression** model. If the test statistic has a ***p* value** less than 0.05, this provides sufficient evidence to reject the null hypothesis that proposes **homoscedasticity** – that is, a constant variance among the residuals. Accordingly, heteroscedasticity can be then assumed (Breusch & Pagan, 1979). In Empirical Research Studies 2 and 3, Breusch-Pagan tests confirmed the presence of heteroscedasticity in the regression models, which supported the use of **quantile regression**.
categorical variable	A variable that comprises two or more values that describe a certain characteristic. Categorical variables can be described as either 'nominal' or 'ordinal'. Nominal categorical variables cannot be ordered; nominal variables with only two possible

	values are called ‘binomial’ variables. Ordinal categorical variables can be arranged according to rank, but the distances between adjacent categories are not equal across the range. Categorical variables with only two values are termed ‘binary’ or ‘dichotomous’ variables. In this thesis, categorical variables were used to describe characteristics of the START cohort and the samples in each of the empirical research studies. In Empirical Research Study 1, the MADRS (which yields scores to produce a continuous variable) was dichotomised and used as a categorical variable. Dichotomisation was undertaken in this study in order to emulate a screening measure, as a binary outcome is a characteristic of a screening tool. Further, dichotomisation was also necessary in order to perform the required **logistic regression** analysis.
condition number; condition index	A method to measure the degree of **multicollinearity** among the **independent variables** in a regression model. The largest condition index is called the condition number. A condition number between 10 and 30 indicates the presence of multicollinearity; when the condition number is larger than 30, the multicollinearity is considered strong (Kim, 2019). The condition index and condition number were used to detect the presence of multicollinearity in Empirical Research Studies 2 and 3; the condition numbers indicated a low degree of interaction between the **independent variables**.
continuous variable	A numerical variable that can assume any value between its minimum and maximum value. In this thesis, continuous variables were used to describe characteristics of the START cohort and the samples in each of the empirical research studies. Further, associations between different continuous variables were explored using **quantile regression** in Empirical Research Studies 2 and 3.
covariate	An independent, confounding variable that can influence the **dependent variable**. Regression models can statistically equalise, or remove, the effects of the covariates, in order to evaluate the independent effect of the variable of interest (Kukull, 2012). In Empirical Research Studies 2 and 3, sex of the stroke survivor, age at stroke onset, and stroke severity were identified as covariates because these factors are known to be associated with recovery outcomes following stroke (Knoflach et al., 2012; Bushnell et al., 2014; Rost et al., 2016).
dependent variable	A variable whose value depends on changes in the **independent variable**. Dependent variables are also referred to as ‘outcome’ or ‘response’ variables. In Empirical Research Study 1, the presence of depressive symptoms was used as the dependent variable in the regression models. In Empirical Research Study 2, scores

	on five different outcome measures were used as dependent variables, in separate regression models. In Empirical Research Study 3, scores on two patient-reported outcome measures were used as the dependent variables, in separate analyses.
descriptive statistics	A term given to describe or summarise the characteristics of a sample or dataset. The two primary types of descriptive statistics are **measures of central tendency** (including mean, median, and mode) and **measures of dispersion** or spread (including standard deviation, range, and interquartile range). Descriptive statistics differ from **inferential statistics** in that their purpose is to summarise and characterise a sample – rather than making inferences about the sample. In this thesis, descriptive statistics were used to describe and summarise the START cohort and the samples in each empirical research study. Descriptive statistics are tabulated and also presented in the main text.
hetero-scedasticity	The condition in which the residuals (or 'error terms') in the relationship between the independent and dependent variable are unequal across all values of the independent variable. This can be represented by a skewed distribution of data on a scatter plot. The presence of heteroscedasticity violates the assumption of an even spread of residuals in ordinary least squares (OLS) regression (Motulsky, 2018). In Empirical Research Studies 2 and 3, the **Breusch-Pagan test** confirmed the presence of heteroscedasticity ($p < 0.05$) in the regression models; this supported the use of **quantile regression**.
homo-scedasticity	Homoscedasticity is the complementary notion of **heteroscedasticity**. Homoscedasticity refers to the condition in which the variance of the residuals (or 'error terms') is constant; that is, the residuals do not vary as the value of the independent variable changes. This can be represented by an even distribution of data on a scatter plot. Homoscedasticity is a standard assumption of OLS regression (Motulsky, 2018). The regression models in Empirical Research Studies 2 and 3 were not homoscedastic, because they were shown to exhibit heteroscedasticity.
independent variable	A variable that causes changes in the **dependent variable**. Independent variables are also referred to as 'explanatory' or 'predictor' variables. In Empirical Research Study 1, time post-stroke was used as the independent variable in the **random effects logistic regression** models. The presence of depressive symptoms at earlier time points was used as the independent variable in the **logistic regression** models. In Empirical Research Study 2, MADRS scores were used as the independent variable in the **quantile regression** models. In Empirical Research Study 3, CCI scores were used as the independent variable in the quantile regression models.

inferential statistics	A term given to statistical methods that enable generalisations and inferences about the population from which the sample is drawn. In this thesis, inferential statistics methods utilised included **logistic regression,** as used in Empirical Research Study 1, and **quantile regression**, as used in Empirical Research Studies 2 and 3.
logistic regression	A statistical analysis used to explore the association between one or more **independent variables** and a **dependent variable** – when the dependent variable is dichotomous or binary. The independent variable may be either categorical or continuous in nature. Logistic regression is also known as 'binomial' or 'binary' logistic regression. Logistic regression yields an odds ratio (*OR)*, allowing the probability of an outcome to be interpreted (Sperandei, 2014). In Empirical Research Study 1, logistic regression was used to explore whether participants with depressive symptoms at earlier time points (independent variable) were more or less likely to experience depressive symptoms at later time points (dependent variable), compared to those without such symptoms.
Mann-Whitney U test	A **non-parametric** statistical test used to compute a *p* value, in order to compare differences between two groups with independent observations. It can be applied when the **dependent variable** is either ordinal or continuous, but not normally distributed (Motulsky, 2018). In all empirical research studies, a Mann-Whitney U test was conducted to compare characteristics of continuous variables between included and non-included participants. A statistically significant difference was observed if $p \leq 0.05$.
measures of central tendency	Summary measures that describe the data with a single value that denotes the centre of the distribution. The three primary measures of central tendency, each describing a different indication of central value, are the mean (M), the median (Mdn), and the mode. In this thesis, the mean and the median were used. The mean was used to describe the central value of parametric data and the median was utilised to denote the centre of non-parametric data.
measures of dispersion	Summary measures that describe the spread or variance of the observations around the central value. These include the standard deviation (*SD*), the range (minimum, maximum), and the interquartile range (IQR). In this thesis, measures of dispersions were reported in conjunction with measures of central tendency to describe the START cohort and samples.
multi-collinearity	Multicollinearity indicates a high degree of interaction between **independent variables** (including **covariates**) in regression models. When two independent variables are highly correlated, they both convey essentially the same information

	resulting in 'collinearity'. When three or more independent variables are entangled in this way, this is referred to as multicollinearity. Multicollinearity can misrepresent the results yielded from regression analyses. Methods to estimate the degree of multicollinearity include the calculation of the condition indices (the **condition number** is the largest of the condition indices) or the **variance inflation factor** (VIF). Multicollinearity may be problematic when the VIF is higher than approximately 5 to 10, or when the CN is higher than approximately 10 to 30 (Kim, 2019). In Empirical Research Studies 2 and 3, the degree of multicollinearity between the **independent variables** (one independent variable and three **covariates**) in each regression model was estimated using the condition number and variance inflation factor.
multiplicity	A term to describe the potential inflation of the type I error rate (which is the rejection of a true null hypothesis) because of multiple, simultaneous analyses conducted on the same sample (Motulsky, 2018). In Empirical Research Studies 2 and 3, the **significance level** was corrected for multiplicity using the **Bonferroni method**; the significance level was set at 0.005 and 0.025, respectively.
non-parametric statistics	Non-parametric statistics does not assume the data is drawn from a normal distribution. Non-parametric statistics are used when the assumptions of parametric tests are violated. The non-parametric tests, **Mann-Whitney U test** and **Pearson's chi-square test**, were used in all empirical research studies. **Quantile regression** is also considered a non-parametric analysis, and was used in Empirical Research Studies 2 and 3.
odds ratio	A measure of association between an exposure and an outcome. The odds ratio (OR) represents the odds or likelihood that an outcome will occur given a particular exposure, compared to the odds or likelihood of the outcome occurring in absence of that exposure. The OR quantifies the strength of association between an exposure and an outcome; if the OR < 1, odds are decreased for the outcome and if the OR > 1, odds are increased for the given outcome. In Empirical Research Study 1, ORs were reported to demonstrate the strength of the association between time post-stroke and the presence of depressive symptoms for each of the **time points dyads**. In addition, the ORs were reported to determine the likelihood of experiencing depressive symptoms at later time points based on depressive symptoms at earlier time points for all three **time point dyads**.
p value	A measure of the probability of observing a particular outcome in the data, by chance, if the null hypothesis is true. The *p* value reflects the strength of evidence

	against the null hypothesis; the smaller the *p* value, the stronger the evidence is to reject the null hypothesis. The *p* value was used in multiple analyses in all empirical research studies.
Pearson's chi-square test	A **non-parametric** statistical test used to compare the distribution of counts of a **categorical variable,** for two or more different populations (Motulsky, 2018). A Pearson's chi-square test was conducted to compare characteristics of categorical variables (such as sex of the stroke survivor) between included and non-included participants in all empirical research studies.
quantile	A quantile is created by the division of the distribution into segments. Quantiles can be referred to as quartiles when the distribution is divided into four equal parts. In Empirical Research Studies 2 and 3, quantile regression models were fitted at the .25, the .5 (the median) and the .75 quantiles.
quantile regression	A statistical method used to explore the association between independent variables, including covariates, and a dependent variable (Koenker & Bassett, 1978). Quantile regression is an extension of linear regression which can be used when the conditions for linear regression are not satisfied (such as the assumption of **homoscedasticity**). Quantile regression estimates the median, and other quantiles, of the dependent variable across the values of an independent variable. Coefficients yielded by quantile regression models are interpreted as the rate of change of the dependent variable, based on a one unit change in the independent variable (Davino et al., 2014). In Empirical Research Studies 2 and 3, quantile regression was employed to explore the association of an **independent variable** (depressive symptoms or comorbidity burden) and **dependent variables** (recovery outcomes).
random effects model	A random effects model is an approach to analyse data collected from the same sample at different points in time (often referred to as 'panel data'). A random effects model accounts for the fact that repeated measurements on individual participants are not statistically independent and may be correlated (Motulsky, 2018). In Empirical Research Study 1, random effects models were used in **logistic regression** to investigate the association between time post-stroke (**independent variable**) and depressive symptoms (**dependent variable**). The individual participants were used as the random effects in this model. Associations between time post-stroke and depressive symptoms were explored, for two **time point dyads**, 3 months versus first week and 12 months versus first week.
regression analysis	An analysis that estimates the relationship between one or more **independent variables** and one **dependent variable**. The most common form of regression is ordinary least squares (OLS) linear regression. The OLS method computes a line that

	most closely fits the data, by minimising the sum of the squares of the vertical distances from the true data to points on the line. Another form is **quantile regression**, which is an extension of linear regression, used when the conditions for linear regression are not met. In Empirical Research Studies 2 and 3, quantile regression was used to estimate the association of an independent variable (depressive symptoms or comorbidity burden) and dependent variables (recovery outcomes).
significance level	A significance level, denoted by alpha (or the symbol 'α'), is a threshold set to determine the strength of evidence required to reject the null hypothesis. The significance level is commonly set to 0.05; it may be set lower, for example when adjusting for **multiplicity.** If a ***p* value** is less than or equal to the predetermined significance level, then the null hypothesis can be rejected – and an association or effect is considered to be statistically significant. In Empirical Research Studies 2 and 3, the significance level was adjusted for **multiplicity** using the **Bonferroni method**; the significance level was set at 0.005 and 0.025, respectively.
time point dyad	A pair of related time points. In Empirical Research Study 1, the three time point dyads explored in the **logistic regression** models were: 'first week and 3 months'; 'first week and 12 months'; and '3 months and 12 months'.
variance inflation factor	A variance inflation factor (VIF) estimates the degree of **multicollinearity** by indicating how much of one **independent variable** is explained by other independent variables (including **covariates**). **Multicollinearity** is considered to be potentially problematic if the VIF is more than approximately 5 to 10 (Kim, 2019). In Empirical Research Study 2, the VIF was calculated to quantify the degree of multicollinearity between the **independent variable** (depressive symptoms) and the **covariates** (age, sex and stroke severity). A mean VIF of 1.07 and 1.05 was observed at 3 and 12 months, respectively. Similarly, in Empirical Research Study 3, the VIF was calculated for the independent variable (comorbidity burden) and the same covariates; a mean VIF of 1.10 was observed at baseline. In both studies, multicollinearity was considered to be low because the VIFs were less than 5.

This chapter presented the common methodology for the empirical research studies presented in this thesis. The study design, measures and statistical methods were described in detail. The next chapter will present demographic and clinical characteristics of the START cohort, which is the source of the data on which the subsequent empirical research studies are based.

Chapter 4.

START Cohort Characteristics

The START collaborative research program yielded data which was utilised in each of the empirical research studies presented in this thesis (Chapters 5, 7 and 8). This chapter describes characteristics related to the START research program, under the following sections:

- 4.1 Study Design Characteristics
- 4.2 Study Cohort Characteristics
- 4.3 Comparison of START Cohort Data with AuSCR Data

4.1 Study Design Characteristics

4.1.1 Hospital recruitment sites (*N* = 19)

Participants were recruited from 19 hospitals throughout Australia and New Zealand: Victoria (6 hospitals), New South Wales (5 hospitals), South Australia (4 hospitals), Queensland (2 hospitals), Western Australia (1 hospital) and Auckland (1 hospital). The majority of participants (74.89%) were recruited from hospitals in Victoria, Australia.

4.1.2 Study workflow

The START research program comprised 219 participants; 100 participants were enrolled via the START PrePARE study arm (Carey et al., 2015) and 119 were enrolled via the START EXTEND study arm (Ma et al., 2012).

4.1.3 Participant Flow

The START PrePARE study arm comprised 100 participants at baseline; this number of participants continued in the study at day 3 to 7, and at 3 months. By 12 months, 3 participants had been lost to follow-up (1 death, 1 withdrawal and 1 uncontactable).

The START EXTEND study arm comprised 119 participants at baseline. Initially, 100 participants were recruited; 19 additional participants were recruited to replace those who had died, withdrawn or who were uncontactable at 3 months. This was undertaken according to the study design in order to meet the predetermined target sample size of 100 participants at the 3 month time point. At day 3 to 7, the number of participants was 116 (3 deaths). By 3 months, the number of participants was 100 (12 deaths, 2 withdrawals and 2 uncontactable). By 12 months, the number of participants was 82 (8 deaths, 2 withdrawals and 8 uncontactable). The participant flow for each study arm is presented in Table 4.1.

Table 4.1

Numbers of Participants at Each Time Point, by Study Arm

Study arm	baseline	day 3 to 7	3 months	12 months
START PrePARE	100	100	100	97
attrition	0	0	0	3 [a]
START EXTEND	119	116	100	82
attrition	0	3 [b]	16 [c]	18 [d]
Total START cohort	219	216	200	179

Note. [a] 1 death, 1 withdrawal, 1 uncontactable. [b] 3 deaths. [c] 12 deaths, 2 withdrawals, 2 uncontactable. [d] 8 deaths, 2 withdrawals, 8 uncontactable.

4.2 Study Cohort Characteristics

4.2.1 Demographic characteristics (*N* = 219)

The mean age at stroke onset was 69.07 (*SD* = 13.07) years and ranged from 27.47 to 94.85 years; 140 (63.93%) were male. The median age at stroke onset was 69.99 (IQR = 18.53; Q1, Q3 = 61.09, 79.62). Most participants (74.89%) resided in Victoria, Australia. When asked about their ethnicity, 53.88 per cent identified as ‘Australian’ or ‘New Zealander’. Approximately half of the participants (53.42%) were retired and 34.25 per cent were employed, at the time of their stroke. Most participants (62.56%) were married or in a defacto relationship; a quarter (24.66%) were separated, divorced or widowed. Most participants (68.04%) were living at home with another person (including a partner, spouse, family member or relative) and 21.00 per cent resided at home on their own. Regarding highest level of education achieved, 39.73 per cent had completed secondary school and 13.70 per cent had completed university (Table 4.2).

Table 4.2

Demographic Characteristics of the Total START Cohort (N = 219)

Demographic Characteristic	***n* (%)**
Sex	
Male	140 (63.93)
Female	79 (36.07)
State/city and country of residence	
Victoria, Australia	164 (74.89)
New South Wales, Australia	32 (14.61)
South Australia, Australia	10 (4.57)
Queensland, Australia	9 (4.11)
Auckland, New Zealand	3 (1.37)
Western Australia, Australia	1 (0.46)
Ethnicity	
Australia or New Zealand	118 (53.88)
Europe	62 (28.31)
Asia	13 (5.94)
Other	13 (5.94)
Unknown or missing	13 (5.94)
Employment	
Retired	117 (53.42)
Employed, paid	58 (26.48)
Self-employed	17 (7.76)
Unable to work/out of work	9 (4.11)
Manages home duties	4 (1.83)
Student	1 (0.46)
Other or unknown	13 (5.94)
Relationship Status	
A married or defacto relationship	137 (62.56)
Separated or divorced	27 (12.33)
Widowed	27 (12.33)
Single	8 (3.65)
Other or unknown	20 (9.13)
Accommodation	
Residing at home, with another	149 (68.04)
Residing at home, alone	46 (21.00)
Retirement village or aged care facility	6 (2.74)
Other or unknown	18 (8.22)
Education, highest level completed [a]	
Primary school (7 years of education completed)	38 (17.35)
Secondary school (13 years of education completed)	87 (39.73)
Technical institute (15 years of education completed)	46 (21.00)
University (16 years of education completed)	30 (13.70)
Unknown	18 (8.22)

Note. [a] The mean number of years of education completed was 12.77 (*SD* = 3.0). In Australia, generally, primary school comprises 7 years (prep, grade 1 through to grade 6); secondary school comprises 6 years (grade 7 through to grade 12); a technical degree usually takes 2 years to complete, and a university degree usually requires 3 years.

4.2.2 Clinical characteristics (*N* = 219)

All participants had an estimated pre-stroke mRS score ≤ 2, as per eligibility criteria for enrolment in the START research program. The majority of participants (85.39%) had an mRS score of 0, indicating no disability prior to the stroke. Regarding comorbidity burden as measured by the CCI, all participants were assigned at least one point for the presence of cerebrovascular disease due to the index stroke. Participants' total CCI scores ranged from 1 to 8. Twenty-four participants (10.96%) had experienced a prior stroke. All participants had an ischaemic stroke, as per eligibility criteria for enrolment in the START program. Of the 219 participants, 210 had recorded NIHSS scores within the first week (day 3 to 7, ± 1 day) (9 missing). The mean score was 5.28 (*SD* = 6.44), the median was 3 (IQR = 6; Q1, Q3 = 1, 7) and scores ranged from 0 to 32. Most participants (73.33%) scored 0 to 6, indicating nil or mild stroke-related neurological severity (Rost et al., 2016). Fifty participants (22.83%) had a history of pre-stroke depression, based on medical records or interview with the patient or family member, and transformed to a PHQ-2 score. Twenty-two participants (10.05%) were taking prescription antidepressant medication at the time of their stroke (Table 4.3).

Table 4.3

Clinical Characteristics of the Total START Cohort (N = 219)

Clinical Characteristic	***n* (%)**
Pre-stroke disability, mRS (0-6)	
0	187 (85.39)
1	31 (14.16)
2	1 (0.47)
Comorbidity burden, stroke onset, CCI (0-35) [a]	
1	57 (26.03)
2	2 (0.91)
3	117 (53.42)
4	9 (4.11)
5	29 (13.24)
6	3 (1.37)
7	0 (0)
8	2 (0.91)
≥ 9	0 (0)
Previous history of stroke	24 (10.96)
Stroke-related neurological severity, day 3 to 7, NIHSS (0-42) [b]	
0-6, category: 'mild' or 'nil'	154 (73.33)
7-16, category: 'moderate'	36 (17.14)
≥ 17, category: 'severe'	20 (9.52)
History of pre-stroke depression, PHQ-2 ≥ 3 (0-6)	50 (22.83%)
Prescribed antidepressants prior to stroke onset	22 (10.05%)

Note. mRS = modified Rankin Scale; CCI = Charlson Comorbidity Index; NIHSS = National Institute of Health Stroke Scale; PHQ-2 = Patient Health Questionnaire 2 item version.

[a] All participants received a score of 1 for the presence of cerebrovascular disease.

[b] NIHSS score categories are based on Rost et al., 2016.

Prevalence of depressive symptoms at each time point

The percentage of participants with depressive symptoms, as measured by MADRS ≥ 7, was 42.20 per cent within the first week, 45.51 per cent at 3 months and 37.58 per cent at 12 months post-stroke (Table 4.4).

Table 4.4

Prevalence of Depressive Symptoms 'Present' in the START Cohort (N = 219)

Time point	Participants with a recorded MADRS score	Participants with depressive symptoms 'present' [a]	%
within the first week	173	73	42.20
3 months	178	81	45.51
12 months	165	62	37.58

Note. [a] MADRS score ≥ 7

4.3 Comparison of START Cohort Data with AuSCR Data

Demographic and clinical characteristics of the START cohort were compared with those of adult registrants in the Australian Stroke Clinical Registry (AuSCR) (Breen et al., 2020). The AuSCR is a collaborative national program that annually collects data relating to acute stroke care and patient health outcomes. The AuSCR provides a standardised approach for hospitals to review and improve stroke care according to national acute stroke care standards. The data published in the 2019 AuSCR report provides information from a total of 20,115 episodes of care for 18,692 adult stroke or transient ischaemic attack patients, from 72 Australian hospitals.

Regarding the location of recruitment sites, the START program comprised 18 hospitals from Australia and one from New Zealand. There were no hospital recruitment sites in Tasmania, Australian Capital Territory or Northern Territory. For the AuSCR program, 72 Australian hospitals contributed to the data. With the exception of the Northern Territory, hospitals in all states participated, as follows: Victoria (29 hospitals), Queensland (21 hospitals), New South Wales (14 hospitals), Tasmania (3 hospitals), South Australia (3 hospitals) and Australian Capital Territory (2 hospitals). All START cohort participants were recruited from hospitals with specialised stroke units. In the AuSCR program, 85 per cent of ischaemic stroke patients were treated in stroke units.

Eligibility to the START program required participants to have had an acute ischaemic stroke – and not any other type of stroke. In comparison, 70 per cent of recorded strokes in the AuSCR database were classified as ischaemic. The age profile of participants in the START cohort (*M* = 69, *SD* = 13 years; *Mdn* = 70; IQR = 19: Q1, Q2 = 61, 80) was younger than that of AuSCR adult registrants (*M* = 73, *SD* = 14 years; *Mdn* = 75; IQR = 19: Q1, Q2 = 65, 84). The START cohort

had a smaller proportion of females (36%) compared with the AuSCR cohort (45%). Enrolment in the START research program required participants to be English-speaking; the majority of AuSCR participants (92%) were recorded as English speakers (Table 4.5). Regarding initial stroke neurological severity, NIHSS scores were stratified differently in the two databases. To facilitate direct comparison, START cohort NIHSS scores were interpolated into categories that matched those of AuSCR data, as follows:

- no symptoms = 0
- minor stroke = 1 to 4
- moderate stroke = 5 to 15
- moderate to severe stroke = 16 to 20
- severe stroke = 21 to 42

In the START research program, an NIHSS score was recorded for 210 participants (at day 3 to 7 post-stroke); this was 96 per cent of the cohort. Twenty-one per cent recorded an NIHSS score of 0 denoting no stroke symptoms. Forty-three per cent had a minor stroke (NIHSS score: 1 to 4); twenty-four per cent had a moderate stroke (NIHSS score: 5 to 15). The remaining 11 per cent had strokes categorised as moderate to severe, and severe (NIHSS score: 16 to 42). In the AuSCR program, an NIHSS score was recorded “on presentation” for 9,348 episodes of ischaemic stroke, which was 46 per cent of all adult registrants (Breen et al., 2020, p. 7). Nine per cent recorded an NIHSS score of 0 denoting no stroke symptoms. Forty per cent had a minor stroke (NIHSS score: 1 to 4); thirty-four per cent had a moderate stroke (NIHSS score: 5 to 15). The remaining 16 per cent had strokes that were moderate to severe, and severe (NIHSS score: 16 to 42) (Table 4.5).

Table 4.5

Comparison of START Cohort Data with AuSCR Data

	START cohort	**AuSCR cohort**
Total number of participants or registrants	219	18,692
Age at stroke onset, years		
M (*SD*)	69 (13)	73 (14)
Mdn (IQR: Q1, Q3)	70 (61, 80)	75 (65, 84)
Female, *n* (%)	79 (36%)	8,157 (45%)
English spoken, *n* (%)	219 (100%) [a]	14,692 (92%)
Ischaemic strokes, *n* (%)	219 (100%) [a]	14,068 (70%) [b]
NIHSS score, by category		
total number	210 [c]	9,348
no stroke symptoms (0)	46 (21%)	840 (9%)
minor stroke (1-4)	91 (43%)	3,771 (40%)
moderate stroke (5-15)	50 (24%)	3,183 (34%)
moderate to severe stroke (16-20)	15 (7%)	786 (8%)
severe stroke (21-42)	8 (4%)	768 (8%)

Note. M = mean; *SD* = standard deviation; *Mdn* = median; IQR = interquartile range; Q1 = Quantile 1; Q3 = Quantile 3. NIHSS = National Institutes of Health Stroke Scale.

[a] Total cohort as per START program eligibility criteria. [b] 14,068 of 20,115 episodes. [c] NIHSS original categories interpolated into new categories for comparison with AuSCR data.

This chapter presented the demographic and clinical characteristics of the START cohort. Further, a comparison was made between the START cohort and the AuSCR cohort to explore the generalisability of the findings from the empirical research studies presented in this thesis. Samples from the START cohort are studied in the Empirical Research Studies 1, 2 and 3, in pursuit of answers to the research questions. These are presented in Chapters 5, 7 and 8.

Chapter 5.
Empirical Study 1: Trajectories and Associations of Depressive Symptoms

Introduction to chapter

The review of longitudinal cohort studies (presented in Chapter 2) explored the trajectories of depression and depressive symptoms of cohorts of stroke survivors, examined separately by result type – frequency or mean score. This review confirmed that post-stroke depression is prevalent and persists into the chronic phase; however, it was difficult to draw definitive conclusions about the trajectory of post-stroke depression. From this review, we recommended that trajectories of the status of post-stroke depression experienced by individuals, within a study cohort, be explored over time. Further, such studies should include multiple assessment time points over a study duration of at least 12 months following stroke onset.

The data from the START cohort (described in Chapter 4) presents an opportunity to undertake these recommendations, and to explore the prevalence and trajectory of depressive symptom status, experienced by individual stroke survivors over the first year following stroke. Further, by using logistic regression modelling (described in Chapter 3), changes and associations in the course of depressive symptom status, over the first year, can be explored. Accordingly, the research questions addressed in this study are:

1. What is the trajectory of depressive symptoms following stroke over time?
2. What are the associations between the presence of depressive symptoms at earlier time points with their presence at later time points?

The prevalence and trajectory of post-stroke depression has implications for the question of screening, which will also be explored in this study.

Trajectories and Associations of Depressive Symptoms at Acute, Subacute and Chronic Phases in a Longitudinal Stroke Cohort

Authors: Katherine Sewell, MPH[1,2], Tamara Tse, PhD[1,3], Leonid Churilov, PhD[4], Henry Ma, PhD[5], Stephen M. Davis, MD[6], Geoffrey A. Donnan, MD[6] and Leeanne M. Carey, PhD[1,2] .

Affiliations:

1. Department of Occupational Therapy, Social Work and Social Policy, School of Allied Health, Human Services and Sport, La Trobe University, Bundoora, Australia
2. Neurorehabilitation and Recovery, Florey Institute of Neuroscience and Mental Health, Heidelberg, Australia
3. Department of Occupational Therapy, St Vincent's Hospital Melbourne, Fitzroy, Australia
4. Melbourne Medical School, University of Melbourne, Melbourne, Australia
5. Department of Medicine, School of Clinical Sciences, Monash University, Melbourne, Australia
6. Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia

Contributions of authors: KS contributed to the conceptualisation, design and methodology of the study; performed the statistical analysis and wrote the manuscript. LMC conceptualised and was the principal investigator for the longitudinal cohort study. LMC and TT contributed to the conceptualisation, design and methodology of the current study and to the writing, reviewing and editing of the manuscript. LC contributed to the statistical methodology and data analysis; verified the interpretation of the results; and provided critical revision of the manuscript. HM, SD and GD reviewed iterations of the manuscripts and provided critical revision. All authors contributed to the final manuscript.

Format: This study has been formatted consistently in the style of this thesis. The figure and tables are included in the body of the manuscript; the supplementary material is presented at the end of this study and chapter. All citations are included in the single reference list at the end of this thesis.

5.1 Abstract

Background: The variable trajectory of post-stroke depression raises questions about the optimal timing for screening, which has not yet been established.

Objectives: To describe and evaluate changes and associations in the course of depressive symptoms within the first year post-stroke.

Methods: This was a prospective, longitudinal, ischaemic stroke cohort study. Participants were assessed within the first week, at 3 and 12 months post-stroke. Depressive symptoms were measured by the Montgomery-Åsberg Depression Rating Scale and dichotomised to either depressive symptoms 'present' (score ≥ 7) or 'absent' (score < 7). Random effects logistic regression was used to investigate the association between time post-stroke and the presence of depressive symptoms. Next, a trajectory diagram was constructed to describe the course of depressive symptom status over time. Last, logistic regression was used to assess the likelihood of participants having depressive symptoms at later time points given their status at earlier time points.

Results: 142 stroke survivors were included for analysis; 68 experienced a change in depressive symptom status from 'present' to 'absent' or vice-versa, during the first year. No evidence of association between time post-stroke and depressive symptom status was observed. Participants with depressive symptoms at 3 months were more likely to have depressive symptoms at 12 months, compared to those without such symptoms at 3 months.

Conclusion: Our findings add to the evidence for the dynamic trajectory of post-stroke depression. The importance of repeated screening for depression is highlighted, not only within the first week but also at later time points, such as at 3 months post-stroke.

5.2 Introduction

Depression is widely recognised as a common consequence of stroke – about 30 per cent of stroke survivors develop depression at some point (Ayerbe et al., 2013a; Hackett & Pickles, 2014). Untreated depression is known to significantly hinder patients' ability to participate in rehabilitation and is associated with poor outcomes (Robinson & Jorge, 2016; Ayerbe et al., 2014). However, post-stroke depression is frequently overlooked (Dar et al., 2017). Its diagnosis can be particularly challenging in stroke survivors, especially those who have residual communication or cognitive impairments (Khan, 2004).

Post-stroke depression varies significantly in onset, course and duration (Ayerbe et al., 2013b). Most episodes of depression start during the first year; one-third are identified within the first 3 months, but for the remaining two-thirds depression does not develop until after 3 months – and may not emerge for many months (Ayerbe et al., 2013b). The variable trajectory of post-stroke depressive symptoms raises questions about the optimal timing for screening, which has not yet been established (Shankar et al., 2017).

Several brief, validated screening measures are available to facilitate the identification of underlying depression. Screening for depression, when undertaken, currently appears to be concentrated within the first few months after stroke (White et al., 2012). However, screening only in the acute phase may result in patients being categorised as 'not depressed', and subsequently not being reviewed at later stages – leading to undetected and untreated depression (Shankar et al., 2017).

Current Australian clinical guidelines recommend that stroke survivors with suspected altered mood be assessed using validated screening tools (National Stroke Foundation, 2021). Further, these guidelines state there is no evidence available regarding the optimal timing of screening for post-stroke depression (National Stroke Foundation, 2021). Concerningly, a recent audit of Australian hospitals managing acute stroke patients reported only 57 per cent had established protocols for evaluating mood (Lynch et al., 2019).

5.2.1 Study Aims

The purpose of this study was to evaluate changes and associations in the course of depressive symptoms in a longitudinal Australian ischaemic stroke cohort – within the first week, at 3 months and at 12 months post-stroke. We aimed to:

i. investigate the association between time post-stroke and the presence of depressive symptoms;
ii. describe the course of depressive symptom status within the first year; and

iii. investigate whether participants with depressive symptoms at earlier time points were more or less likely to experience depressive symptoms at later time points, compared to those without such symptoms.

5.3 Methods

5.3.1 Study design

The study was a prospective, observational, longitudinal cohort design. Participants were recruited via the Stroke Imaging Prevention and Treatment (START) collaborative research program which comprised two arms. Patients recruited within 3 days post-stroke were entered into the Prediction and Prevention to Achieve optimal Recovery Endpoints after stroke (START PrePARE) arm (Carey et al., 2015). Those recruited 4.5 to 9 hours post-stroke, if eligible, were enrolled into the Extending the Time for Thrombolysis in Emergency Neurological Deficits (START EXTEND) arm (Ma et al., 2012). Informed consent by the participant, or legally responsible person, was required for participation. The study was approved by ethics committees at each recruiting hospital site and tertiary institution.

5.3.2 Participants

Participants were recruited consecutively from hospitals throughout Australia and New Zealand, all of which had specialised stroke units, between June 2010 and April 2013. Eligibility criteria required participants to be diagnosed with acute ischaemic stroke, aged 18 years or older, English-speaking, and with no significant premorbid disability as determined by an estimated modified Rankin Scale (mRS) score ≤ 2 (Bonita & Beaglehole, 1988). Additional inclusion criteria for thrombolysis were required for participants recruited through the START EXTEND arm (Ma et al., 2012).

5.3.3 Procedure

Participants were assessed at three time points: within the first week (3 to 7 days, ± 1 day), at 3 months (± 7 days) and at 12 months (± 7 days) following stroke. These time points align with key post-stroke phases described in recovery frameworks and underpinned by knowledge of the biology of stroke recovery (Carey & Seitz, 2007; Carey et al., 2015; Bernhardt et al., 2017). In our study, the first time point corresponds with the ‘acute’ phase (1 to 7 days). Our second time point corresponds with the midpoint of the ‘early subacute’ (7 days to 3 months) and ‘late subacute’ (3 to 6 months) phases. Our third time point relates to the ‘chronic’ phase (more than 6 months).

5.3.4 Measures

Outcome measures were administered by health professionals at each participant's treating hospital or home. Data collected on admission included: age, sex, prior history of stroke and premorbid disability. The National Institutes of Health Stroke Scale (NIHSS) was used to evaluate stroke severity within the first week (day 3 to 7, ± 1 day) (Brott et al., 1989).

The Montgomery-Åsberg Depression Rating Scale (MADRS) was utilised to determine depressive symptom status at each time point. MADRS items focus on core mood symptoms, in contrast to other screening tools that include items relating to somatic symptoms and motor retardation (Montgomery & Åsberg, 1979). Somatic symptoms may be attributable to physical, rather than psychological, sequelae of stroke; the detection of such symptoms may overestimate the presence of depressive symptoms, particularly in the acute phase (Lökk & Delbari, 2010). The MADRS comprises ten items, each scored from 0 to 6; higher scores indicate more severe depressive symptoms (Montgomery & Åsberg, 1979).

We used the Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA) in the administration of the MADRS, which asks about mental state over the preceding week. The MADRS SIGMA has been validated in stroke cohorts and has yielded high inter-rater reliability (intraclass correlation coefficient of 0.93) (Williams & Kobak, 2008). This was important in our study in order to standardise its use by multiple assessors across multiple locations. Total MADRS scores were dichotomised into depressive symptoms 'present' (score ≥ 7) or 'absent' (score < 7) (Hackett et al., 2005).

5.3.5 Data analysis

Participants for whom a MADRS score was recorded at all three time points were included for analysis. Characteristics of included participants were compared with those non-included using Mann-Whitney U tests for continuous variables and Pearson's chi-square tests for categorical data. First, to investigate the association between time post-stroke and the presence of depressive symptoms, we used random effects logistic regression. Time post-stroke was used as the independent variable: within the first week (reference category), at 3 months and at 12 months. We used the presence of depressive symptoms as the dependent variable and individual patients as random effects. Next, to describe the course of depressive symptom status within the first year, a trajectory diagram was constructed and analysed. Last, to investigate whether participants with depressive symptoms at earlier time points were more or less likely to experience depressive symptoms at later time points, compared to those without such symptoms, we used logistic regression modelling. The presence of depressive symptoms at earlier time points was used as the independent variable, and their presence at later time points was used as the dependent variable. We applied the models for the following time point dyads: first week versus 3 months; first week versus 12 months; and 3 months versus 12 months. For each time point dyad, we reported the

odds ratio (*OR*), corresponding 95 per cent confidence interval (95% CI) and *p* values uncorrected for multiplicity; $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using Stata version 16.1 (StataCorp, 2019).

5.4 Results

5.4.1 Participants

The sample comprised 142 ischaemic stroke survivors who had a MADRS score recorded at all three time points; this represented 64.8 per cent of the 219 participants from the START cohort. Reasons for attrition between baseline and 12 months included: withdrawal (4 participants); loss of contact (10 participants) and death (21 participants).

Of the 142 participants, 96 (67.6%) were male; mean age at stroke was 67 (*SD* = 13), range 27 to 91 years. Sixteen (11.3%) had a previous history of stroke. The majority (87.3%) had no pre-stroke disability (mRS = 0). The median NIHSS score (day 3 to 7, ± 1 day) was 2 (IQR: Q1, Q3 = 0, 3). The median MADRS score within the first week was 5 (IQR: Q1, Q3 = 1, 10]; at 3 months was 5 (IQR: Q1, Q3 = 1, 11] and at 12 months was 4 (IQR: Q1, Q3 = 0, 10) (Table 5.1).

Table 5.1

Demographic and Clinical Characteristics of Sample (n = 142)

		***M* (*SD*) / frequency**	**range (min., max.) / %**	***Mdn* (IQR: Q1, Q3)**
age at stroke onset, years		66.96 (13.12)	27.47, 90.72	67.89 (60.40, 77.97)
sex, male		96	67.61%	
previous history of stroke		16	11.27%	
estimated pre-stroke disability (mRS, 0-6)				
0		124	87.32%	
1		18	12.68%	
2		0	0.0%	
neurological deficit, day 3-7 (NIHSS, 0-42)		2.73 [a] (3.64)	0, 18	2 (0, 3)
0-6	*mild*	127	89.44%	
7-16	*moderate*	11	7.75%	
17-42	*severe*	3	2.11%	
missing		1	0.70%	
depressive symptoms (MADRS SIGMA, 0-60)				
first week		6.57 (6.86)	0, 38	5 [1; 10]
3 months		7.06 (7.38)	0, 33	5 [1; 11]
12 months		6.20 (6.68)	0, 29	4 [0; 10]

Note. mRS = modified Rankin Scale: NIHSS = National Institutes of Health Stroke Scale; MADRS SIGMA = Montgomery-Åsberg Depression Rating Scale Structured Interview Guide; *M* = mean; *SD* = standard deviation; *Mdn* = median; IQR = interquartile range; Q1 = Quantile 1; Q3 = Quantile 3

[a] NIHSS score missing for 1 participant, n=141.

Characteristics of included and non-included participants

The included sample was significantly younger (n = 142; mean age = 67, SD = 13 years) and had significantly milder strokes (median NIHSS score = 2, IQR = 3) in comparison to those non-included (n = 77; mean age = 73, SD = 12 years; median NIHSS score = 10, IQR = 12). There were no significant differences between subgroups in relation to sex, previous history of stroke or premorbid disability (Table 5-S1, supplement).

5.4.2 Association between time post-stroke and presence of depressive symptoms

Random effects logistic regression models demonstrated no evidence of association between time post-stroke and presence of depressive symptoms for the dyads: 3 months versus first week (OR 1.30, 95% CI [0.73, 2.33]; p = 0.375) and 12 months versus first week (OR 0.80, 95% CI [0.44, 1.44]; p = 0.453) (Table 5.2).

Table 5.2

Association Between Time Post-Stroke and Presence of Depressive Symptoms for Time Point Dyads

Presence of depressive symptoms compared to the first week	**OR [95% CI]**	***p***
3 months	1.30 [0.73, 2.33]	0.375
12 months	0.80 [0.44, 1.44]	0.453

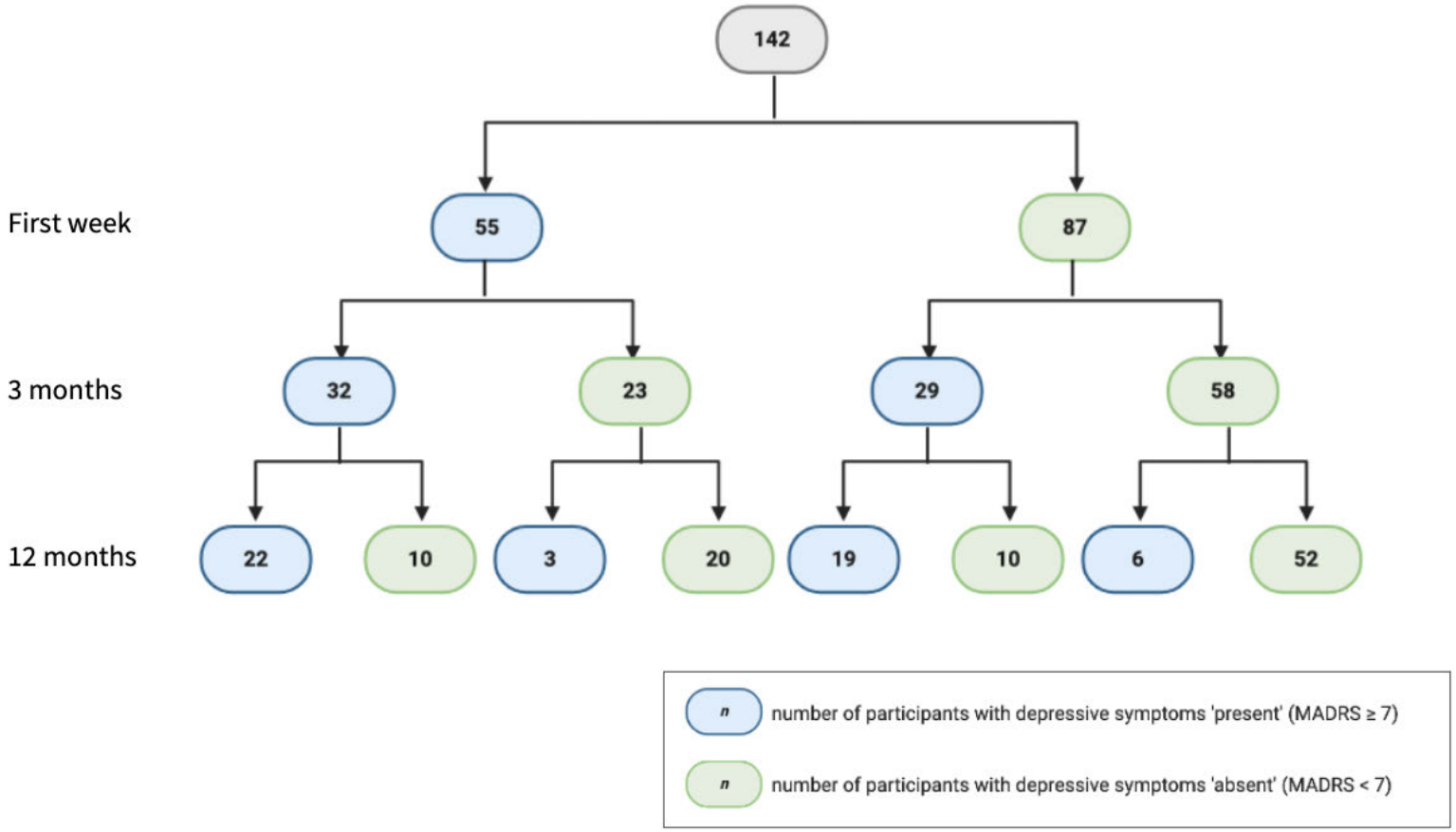
Note. OR = odds ratio; CI = confidence interval

5.4.3 Trajectories of depressive symptom status

Ninety of 142 (63.4%) participants experienced depressive symptoms at one or more time points. The percentage of participants with depressive symptoms at each time point were 38.7 per cent, 43.0 per cent and 35.2 per cent respectively. Eighty-seven (61.3%) participants were assessed as not having depressive symptoms during the first week; however, of these, 29 and 25 experienced depressive symptoms at 3 and 12 months respectively. At 12 months, 50 (35.2%) participants were assessed as having depressive symptoms. Half of these (25 of 50) had depressive symptoms within the first week, whereas a higher proportion (41 of 50) had such symptoms at 3 months. Sixty-eight participants demonstrated a change in depressive symptom status from ‘present’ to ‘absent’ or vice-versa, during the first year after stroke (Figure 5.1).

Figure 5.1

Trajectories of Depressive Symptom Status During the First Year Post-Stroke



5.4.4 Likelihood of experiencing depressive symptoms at later time points based on depressive symptom status at earlier time points

Logistic regression models demonstrated that participants with depressive symptoms within the first week were somewhat more likely to have depressive symptoms, compared to participants without such symptoms within the first week, at both 3 months (*OR* = 2.78, 95% CI [1.39, 5.59]; *p* = 0.004) and 12 months (*OR* = 2.07, 95% CI [1.02, 4.18]; *p* = 0.044). Notably, participants with depressive symptoms at 3 months were much more likely to experience depressive symptoms at 12 months, compared with those without such symptoms at 3 months (*OR* = 16.40, 95% [6.84, 39.35]; *p* < 0.001) (Table 5.3).

Table 5.3

Likelihood of Experiencing Depressive Symptoms at Later Time Points Based on Depressive Symptoms Status at Earlier Time Points

Later Time Point	Earlier Time Point	OR [95% CI]	*p*
3 months	First week	2.78 [1.39, 5.59]	0.004
12 months	First week	2.07 [1.02, 4.18]	0.044
12 months	3 months	16.40 [6.84, 39.35]	<0.001

Note. OR = odds ratio; CI = confidence interval

5.5 Discussion

5.5.1 Overview of study findings

In this sample of ischaemic stroke survivors, we have demonstrated the dynamic trajectory of depressive symptoms across the acute, subacute and chronic phases, within the first year post-stroke. Most (89.4%) participants had mild neurological deficits (NIHSS score ≤ 6, day 3 to 7) (Rost et al., 2016), despite efforts to support the inclusion of patients with severe neurological impairments in this study. Random effects logistic regression models did not show evidence for an association between time post-stroke and the presence of depressive symptoms. The trajectory analysis supported this finding by demonstrating that the proportion of stroke survivors with depressive symptoms, at each time point, was consistently high. Importantly, however, almost half (23 of 55) of participants with depressive symptoms within the first week were no longer categorised as having these symptoms at 3 months. In contrast, most (41 of 50) participants with depressive symptoms at 12 months had been categorised as having such symptoms at 3 months. Logistic regression models supported these findings by demonstrating that participants with depressive symptoms at 3 months were much more likely to have depressive symptoms at 12 months – compared to those without such symptoms at 3 months.

5.5.2 Possible explanation for our findings

We considered possible explanations for our finding that participants with depressive symptoms at 3 months (subacute phase) were more likely to have depressive symptoms at 12 months (chronic phase), compared to those without such symptoms at 3 months. We postulate that by the subacute phase many patients will have been discharged or transferred from acute hospital settings to rehabilitation services, to supported residential care or to their homes. Depressive symptoms may not become apparent until at, or after, these transitions – when stroke survivors attempt to resume participation in their usual daily activities and roles (Tellier & Rochette, 2009). The association between depressive symptoms with reduced participation in social and household activities at 12 months post-stroke has been established (Tse et al., 2019).

In the acute phase, stroke survivors may not have become fully aware of the extent of their limitations due to cognitive impairment and may therefore deny depressive symptoms (Gaete & Bogousslavsky, 2008). By the subacute phase, however, they are more likely to have become aware of any residual stroke-related deficits and longer-term impacts (White et al., 2012), contributing to the apparent latency of onset of post-stroke depression in many cases.

We also considered reasons for the comparatively lower likelihood of depressive symptoms at later phases when such symptoms were present in the acute phase. We suggest that there may be psychological symptoms, other than those due to depression, detected during the acute phase. The nature of stroke is sudden, complex and potentially catastrophic, which distinguishes it from other, more insidious medical conditions. Stroke survivors are often confronted with potential loss of independence, loss of role and social isolation (Salter et al., 2008). This may contribute to the acute emergence of grief, anxiety and uncertainty which mimic, or overlap with, symptoms of depression. These symptoms have been described in the literature as acute 'grief response' (Hermann & Wallesch, 1993) or 'pseudo-depressive manifestations' (Dafer et al., 2008).

5.5.3 Our findings in the context of current literature

Other longitudinal cohort studies have examined the course of post-stroke depressive symptoms. Notably, the South London Stroke Register demonstrated dynamic trajectories of depression at 3 months, one year and annually thereafter, up to 15 years post-stroke (Ayerbe et al., 2013b). Our findings add to the evidence that the course of depressive symptoms following stroke is dynamic, in timing of onset and trajectory. Our study included an assessment in the acute phase (within the first week); two other studies also used very early time points, although neither was continued beyond 3 months (Townend et al., 2007; Shankar et al., 2017). Both studies observed low prevalence, in their respective cohorts, of depressive symptoms within the first week, with much higher prevalence noted in the subacute phase. They concluded that patients with depressive symptoms in the acute phase were not necessarily the ones affected in the subacute phase

(Townend et al., 2007) and questioned the usefulness of screening for depression in acute hospital settings (Shankar et al., 2017). Several other studies have also shown high prevalence and variability of post-stroke depression over time (Berg, 2003; Allan, 2013; Bour, 2010; Shi, 2015; Eriksen, 2016; Kim & Kim, 2016; Li et al., 2019). However, it is difficult to draw comparisons because they differed substantially from our study, and from each other, in their primary aims, cohort characteristics, assessment methods and time points used.

5.5.4 Our findings in the context of current international guidelines

Clinical practice would benefit from more explicit guidelines regarding both the optimal timing and frequency of screening for post-stroke depression. The American Stroke Association recommends routine administration of a structured depression inventory following stroke; however, this organisation also states there is a need for further research to determine the ideal timing of screening (Powers et al., 2019; Towfighi et al., 2017). The Canadian Stroke Best Practices Recommendations advise the assessment of all stroke patients for depression, repeatedly, including beyond the acute phase. These guidelines state that the optimal timing of screening for depression is currently unclear but suggest screening at transition points: at transfer from acute settings to rehabilitation services; at discharge to the community; at follow-up appointments and at reviews with primary care practitioners (Heart and Stroke Foundation of Canada, 2018). In the United Kingdom, the National Clinical Guideline for Stroke recommends screening for mood disorders at multiple time points: during the acute phase, at transfer into post-acute services, at 6 months and at 12 months post-stroke (Royal College of Physicians, 2016). Our findings are consistent with recommendations for repeated screening for post-stroke depression, beyond the acute phase.

5.5.5 Study limitations

Included participants differed significantly from those non-included in age and stroke severity (Table 5-S1, supplement). Our sample had a lower mean age at stroke and lower proportion of females compared with national figures published by the Australian Stroke Clinical Registry (mean age = 73 years, *SD* = 13; females 45%). All our participants had ischaemic stroke, based on inclusion criteria, whereas 70 per cent of registry patients had ischaemic stroke (Breen et al., 2020). All our participants were recruited from hospitals with specialised stroke units, which may have contributed to better outcomes. Next, the MADRS yields scores which produce a continuous variable; however, in our study the scores were dichotomised. Such dichotomisation of continuous variables is known to have the disadvantage that scores which are close, but on opposite sides of the cut-off, are characterised as different when they may represent patients whose characteristics are similar. However, the purpose of screening tools with validated cut-off points is to produce a binary outcome to inform the decision whether or not to conduct further

assessment. Last, our study does not report, nor adjust for, participants who had previously had depression, or who received treatment for depression during the study.

5.5.6 Recommendations for future research

To advance our understanding of trajectories of post-stroke depression, we recommend further research utilising screening in prospective, longitudinal, cohort studies, lasting at least one year. We suggest focusing on multiple time points throughout acute, subacute and chronic phases – and also at transition points across the continuum of care. A better understanding of the trajectories of post-stroke depression would help to determine the optimal timing and frequency of screening for post-stroke depression.

5.5.7 Implications for clinical practice

Clinicians should be aware that depressive symptoms after stroke are common and often follow a variable course throughout the first year. We suggest screening for depression not only in the acute phase, but also during subacute and chronic phases. Our findings highlight the value of screening at 3 months, at which time there is a high proportion of stroke survivors with depressive symptoms – and an association with persisting depressive symptoms at 12 months. This may have relevance to the 3 month time point which lies within the subacute phase of the temporal frameworks of stroke recovery, during which there is evidence for increasing neural plastic change and functional improvement (Carey & Seitz, 2007; Bernhardt et al., 2017). Further, we recommend that stroke survivors who meet the threshold for depressive symptoms 'present' using a validated screening tool should be referred for formal psychiatric assessment. Last, we recommend that stroke clinical practice guidelines be reviewed and updated, to advise on the optimal timing and frequency of screening for post-stroke depression.

5.6 Conclusion

In our study, approximately half of stroke survivors varied in their status of depressive symptoms during the first year – which adds to the evidence for the dynamic trajectory of post-stroke depression. Participants with depressive symptoms at 3 months (subacute phase) were much more likely to have depressive symptoms at 12 months (chronic phase) – compared to those without such symptoms at 3 months. Our study highlights the importance of repeated screening for post-stroke depression, not only in the acute phase but also at later phases, such as 3 months post-stroke.

Supplementary Material

Table 5-S1.

Demographic and Clinical Characteristics of Included and Non-Included Participants

	included (n=142)	**non-included (n=77)**	
	mean (*SD*) / frequency	**mean (*SD*) / frequency**	***p***
age at stroke onset, years	66.96 (13.12)	72.98 (12.10)	**0.002**[a]
sex, male	96	44	0.124
previous history of stroke	16	8	0.843
pre-stroke disability (mRS, 0-6)			
0	124	63	
1	18	13	0.266
2	0	1	
	Mdn [IQR: Q1; Q3]	*Mdn* [IQR: Q1; Q3]	*p*
neurological deficit, day 3-7 (NIHSS, 0-42)	2 [0; 3] [b]	10 [4;16] [c]	**<0.001**[a]

Note. mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; *SD* = standard deviation; *Mdn* = median; IQR = interquartile range; Q1 = Quantile 1; Q3 = Quantile 3.
Included participants were compared with those non-included using the Mann-Whitney U test for continuous variables and Pearson's Chi-square test for categorical data.
[a] statistically significant result. [b] NIHSS score missing for 1 participant, n = 141. [c] NIHSS score missing for 8 participants (n = 69).

Chapter 6.
Perspective: Screening for Post-Stroke Depression

Introduction to chapter

The preceding chapter, Empirical Research Study 1 (Chapter 5) added to current literature by demonstrating a high prevalence and a dynamic trajectory of post-stroke depression over the course of the first year following stroke, within an Australian cohort. This emerging evidence for the dynamic trajectory of post-stroke depression excited curiosity about current clinical practice regarding screening for depression in stroke populations. Preliminary exploration revealed that in practice, in Australia, there is a paucity of established protocols for evaluating mood in stroke patients. There may be a large number of stroke patients with undetected and untreated depression.

As clinical practice is informed by guidelines, current recommendations for the screening of post-stroke depression were also explored. Australian guidelines regarding post-stroke depression state there is a lack of evidence for routine screening and that recommendations about who should be screened, and when, cannot be made. Accordingly, the Perspective Article included in this thesis poses three questions:

- Who should be screened?
- When should we screen?
- How should we screen?

This Perspective Article addresses these questions, and based on our suggested responses, recommends that current Australian stroke management guidelines be reviewed and updated.

The research question for the Perspective Article is: What is current Australian clinical practice regarding screening for post-stroke depression?

Screening for Post-Stroke Depression – Who, When and How? What Australia Can Learn from International Guidelines

Authors: Katherine Sewell, MPH[1,2], Tamara Tse, PhD[1,3], Geoffrey A. Donnan, MD[4] and Leeanne M. Carey, PhD[1,2] .

Affiliations:

1. Department of Occupational Therapy, Social Work and Social Policy, School of Allied Health, Human Services and Sport, La Trobe University, Bundoora, Australia
2. Neurorehabilitation and Recovery, Florey Institute of Neuroscience and Mental Health, Heidelberg, Australia
3. Department of Occupational Therapy, St Vincent's Hospital Melbourne, Fitzroy, Australia
4. Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia

Contributions of authors: KS designed and wrote the manuscript. TT, GD and LC provided substantive feedback throughout the iterative process.

Publication status: Accepted for Publication in the Medical Journal of Australia (30 April 2021).

Citation: Sewell K, Tse T, Donnan GA, et al. Screening for Post-Stroke Depression – Who, When and How?. *Med J Aust* 2021; in press.

Permission: Permission to use the Perspective Article, presented in Chapter 6 in this dissertation, was granted by the Senior Publishing Coordinator at the Medical Journal of Australia via email correspondence on 12 August 2021 (Appendix S).

Format This Perspective Article has been formatted consistently in the style of this thesis, independent of the style required by MJA. All in-text citations of this study are included in the single reference list at the end of this thesis.

6.1 Introduction

Depression is a common sequela of stroke; approximately 30 per cent of stroke survivors develop depression (Hackett & Pickles, 2014). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) recognises post-stroke depression within the category 'Depressive Disorder Due to Another Medical Condition' (American Psychiatric Association [APA], 2013a). Post-stroke depression significantly hinders patients' ability to participate in rehabilitation and is associated with poor health outcomes. Despite its high prevalence and negative impact, post-stroke depression is vastly underdiagnosed (Medeiros et al., 2020). One estimate suggested that only five per cent of stroke survivors are diagnosed with, and treated for, depression in routine clinical practice (Swartz et al., 2016). Diagnosis of depression can be challenging in stroke survivors, especially in those who have residual communication and cognitive impairments.

Post-stroke depression varies significantly in timing of onset, course and duration. Most episodes start during the first year; one-third are identified within the first three months. For the remaining two-thirds, however, depression does not develop until after three months post-stroke and may not emerge until many months later (Ayerbe et al., 2013b). The dynamic and variable trajectory of depression after stroke raises questions about the optimal timing and setting for screening – which have not yet been established (Towfighi et al., 2017).

6.2 Current Australian Guidelines

In Australia, the Stroke Foundation is the peak body that coordinates and disseminates national clinical guidelines for stroke management. Their current guideline regarding mood disturbance following stroke states that "stroke survivors with suspected altered mood … should be assessed by trained personnel using a standardised and validated scale" (National Stroke Foundation, 2021, para. 'Mood Assessment'). Furthermore, the 'section text' attached to this guideline states "there is a lack of evidence about whether routine screening for depression outweighs the potential harms, or is cost effective, therefore specific recommendations about who should be screened and when cannot be made" (National Stroke Foundation, 2021, para. 'Mood Disturbance'). This statement is supported by a single citation, a meta-analysis of 16 randomised controlled trials, which examined the effectiveness of screening and case-finding in the recognition of depression (Gilbody et al., 2008). However, the studies included in the analysis predominantly comprised cohorts from general practice and primary care settings. The authors commented that the prevalence of depression is low, less than 10 per cent, in unselected populations (Gilbody et al., 2008). Although it seems likely these cohorts would have included at least some stroke patients, none were specifically stroke cohorts – where the prevalence of depression is known to be higher than in the general population.

In practice, there may be large numbers of stroke patients with undetected depression. An audit of Australian hospitals managing acute stroke patients reported only 57 per cent had established protocols for evaluating mood (Lynch et al., 2019). The Stroke Foundation's National Stroke Audit Rehabilitation Services Report 2020 stated that only 63 per cent of stroke survivors from the participating rehabilitation services had undergone mood assessment. Concerningly, of those assessed who were identified as having a mood disorder, two-thirds were not provided with any further intervention (National Stroke Foundation, 2020). It is possible that some patients' symptoms had resolved at a subsequent re-assessment and treatment was not required; however, this information was not captured by the audit.

6.3 International Guidelines

We searched international websites for published clinical guidelines regarding the detection of post-stroke depression. The American Stroke Association recommend routine administration of a structured depression inventory following stroke; however, this organisation also states there is a need for further research to determine the ideal timing of screening (Towfighi et al., 2017; Powers et al., 2019). The Canadian Stroke Best Practices Recommendations advise the assessment of all stroke patients for depression, repeatedly – including beyond the acute phase. These guidelines state that the optimal timing of screening for depression is currently unclear but suggest screening at transition points: at transfer from acute settings to rehabilitation services, at discharge to the community, at follow-up appointments and at reviews with primary care practitioners (Heart and Stroke Foundation of Canada, 2019). In the United Kingdom, the National Clinical Guideline for Stroke recommends screening for mood disorders within the first 6 weeks, at transfer into post-acute services and at follow-up at 6 and 12 months (Royal College of Physicians, 2016).

6.4 Is it Time for Updated Australian Guidelines and Practice?

We recommend that the current Australian guidelines regarding the identification of post-stroke depression should be reviewed and updated. We suggest the following questions should be considered in their redevelopment – and we offer our responses to these questions.

Who should we screen? Routine screening for all stroke survivors.

Post-stroke depression is a condition that is eminently suitable for routine screening. Criteria for conditions for which routine screening is appropriate include (The Royal Australian College of General Practitioners, 2016):

- The condition is an important health problem
- It has reasonably high prevalence
- It has a detectable latent phase
- There are validated screening measures with defined cut-off scores
- The screening measures are relatively brief and easy to administer

- The use of screening measures is acceptable to the target population
- There are effective treatments for the condition
- The benefits of screening outweigh any potential harm

The current Stroke Foundation guideline appears to recommend a selective screening or a case-finding approach – rather than routine screening of all stroke patients. One problem with this approach is that it requires a clinician to decide which individuals they suspect might be depressed. However, as the Stroke Foundation guideline states "… clinicians find it difficult to detect symptoms of mood disorders" (Gilbody et al., 2008). Relying on selective screening or case-finding risks missing depression in many stroke survivors, given the high prevalence and variable course of post-stroke depression. In comparison, the Australian National Heart Foundation recommends routine screening for depression of all coronary heart disease patients, where the prevalence of depression is also high, ranging from 15 to 40 per cent (Colquhoun et al., 2013).

When should we screen? Repeatedly, beyond the acute phase.

Our current national guidelines state there is a lack of evidence available regarding the optimal timing for screening for post-stroke depression (National Stroke Foundation, 2021). Screening only in the acute phase may lead to many patients being categorised as 'not depressed', with the possibility thereafter of inadvertently not being reviewed, and subsequently experiencing undetected depression. During the subacute phase, many patients will have been discharged or transferred from the acute hospital setting to a rehabilitation service, to supported residential care, or to their home. Depressive symptoms may not become apparent until after these transitions, when stroke survivors attempt to resume participation in their usual daily activities and roles. There is evidence for variation in the timing of onset and course of post-stroke depression (Ayerbe et al., 2013b), therefore repeated screening should be considered.

How should we screen? Validated screening measures.

There are many validated questionnaires available which assess for the presence and severity of depressive symptoms. Most are patient-reported and can be completed by patients themselves, or by family members on patients' behalf – Beck Depression Inventory (BDI, 21 items), Center for Epidemiological Studies Depression Scale (CES-D, 20 items), Geriatric Depression Scale (GDS, 15 or 30 item versions), Hospital Anxiety and Depression Scale – Depression subscale (HADS-D, 7 items) and Patient Health Questionnaire (PHQ, 2- or 9-item versions). Other measures were originally designed to be completed by health professionals by interview with, and observation of, patients – Hamilton Depression Rating Scale (HDRS, 17 items) and Montgomery-Åsberg Depression Rating Scale (MADRS, 10 items), both of which have structured interview guides available. Further, some screening tools have online versions and the PHQ has a smart phone

version which facilitate their availability and use. Online and smart phone versions of patient-reported screening measures can be used independently by patients without significant dysphasia or cognitive impairment.

These questionnaires yield scores on continuous scales, but when used as screening measures are dichotomised at validated cut-off scores in order to identify those most at risk of having depression. It is recognised that screening tools may not be able to distinguish between the symptoms of post-stroke depression and those of other psychological or neuropsychiatric sequelae of stroke, such as emotional lability, grief and anxiety. Nonetheless, the purpose of screening measures is to identify patients most at risk of post-stroke depression, the definitive diagnosis of which requires a comprehensive psychiatric interview.

Routine screening can be undertaken by a range of health professionals, including nurses, occupational therapists, psychologists, general practitioners or medical specialists. The time required to administer these questionnaires does vary but is generally brief, in the approximate range of 5 to 20 minutes. Screening can take place in a variety of settings, such as in acute hospitals, in rehabilitation centres, in residential care, at patients' homes or in GP clinics.

If a stroke survivor meets the threshold on a validated screening tool, it is recommended that the patient undergoes formal psychiatric assessment. The clinical diagnosis of post-stroke depression requires expert history-taking and an in-depth mental state examination, conducted by a trained practitioner to assess for the presence of specific criteria outlined in the DSM (APA, 2013a). Decisions about subsequent management, including periodic re-assessment, can then be made by treating clinicians.

6.5 Recommendations for Updating Australian Guidelines

We recommend an update in Australian guidelines promoting the routine screening of all stroke survivors for depressive symptoms – not just those with suspected altered mood. Further, we recommend these guidelines advise that screening should be undertaken repeatedly, at appropriate intervals. It is important to screen not only in the acute phase, but also at subacute and chronic phases; most practically at least at transition points along the continuum of care – as is advised by Canadian (Heart and Stroke Foundation of Canada, 2019) and UK (Royal College of Physicians, 2016) guidelines.

Chapter 7.

Empirical Study 2: Depressive Symptoms and Recovery Outcomes

Introduction to chapter

The previous chapters (Chapters 5 and 6) highlighted the need for routine and repeated screening for post-stroke depression because it is common and has a variable course. The Empirical Research Study presented in this chapter focuses on why the detection of post-stroke depression is important. There is a considerable body of research that demonstrates the impact of depression on recovery following stroke. Measuring recovery, however, is difficult because 'overall recovery' is multidimensional and complex. There does not appear to be a widely accepted, conceptual definition of 'overall recovery' in stroke literature. When definitions of recovery have been suggested, these appear to focus on functional recovery and motor recovery – and seldom consider psychological, social and contextual factors. The preponderant use of functional recovery outcome measures may misrepresent what constitutes a 'successful' recovery. The aim of Empirical Research Study 2 was to explore the association between depressive symptoms and recovery post-stroke – using several different outcome measures, all commonly used in stroke practice and research.

The research question for Empirical Research Study 2 is: What is the association between depressive symptoms and recovery, over the first year following stroke, using various recovery outcome measures?

Depressive Symptoms are Associated with Patient Perceived Recovery Outcomes at 3 and 12 months Post-Stroke

Authors: Katherine Sewell, MPH[1,2], Tamara Tse, PhD[1,3], Leonid Churilov, PhD[4], Thomas Linden, PhD[2,5], Sheila Crewther, PhD[6], Henry Ma, PhD[7], Stephen M. Davis, MD[8], Geoffrey A. Donnan, MD[8] and Leeanne M. Carey, PhD[1,2] .

Affiliations:

1. Department of Occupational Therapy, Social Work and Social Policy, School of Allied Health, Human Services and Sport, La Trobe University, Bundoora, Australia
2. Neurorehabilitation and Recovery, Florey Institute of Neuroscience and Mental Health, Heidelberg, Australia
3. Department of Occupational Therapy, St Vincent's Hospital Melbourne, Fitzroy, Australia
4. Melbourne Medical School, University of Melbourne, Melbourne, Australia
5. Institute of Neuroscience and Physiology, Gothenburg University, Gothenburg, Sweden.
6. School of Psychology and Public Health, La Trobe University, Melbourne, Australia.
7. Department of Medicine, School of Clinical Sciences, Monash University, Australia
8. Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia

Contributions of authors: KS contributed to the conceptualisation, design and methodology of the study, performed the statistical analysis and wrote the manuscript. LMC conceptualised and was the principal investigator for the longitudinal cohort study. LMC and TT contributed to the conceptualisation, design and methodology of the current study, and to the writing, reviewing and editing of the manuscript. LC contributed to the statistical methodology and data analysis of the data, verified the interpretation of the results, and provided critical revision of the manuscript. HM, SD, GD, TL and SC reviewed iterations of the manuscripts and provided feedback. All authors contributed to the final manuscript.

Format: This study has been formatted consistently in the style of this thesis. The tables are presented in the body of the manuscript and the supplementary material is included at the end of this study. All in-text citations of this study are included in the single reference list at the end of this thesis.

7.1 Abstract

Background: Post-stroke depressive symptoms are common and are associated with poorer recovery outcomes. However, measuring recovery post-stroke is complex.

Objective: To explore the association between depressive symptoms and outcomes, at 3 and 12 months post-stroke, using a profile of recovery measures.

Methods: We conducted a prospective, longitudinal study of ischaemic stroke survivors. Measures used were: Montgomery-Åsberg Depression Rating Scale (MADRS); three variants of the Stroke Impact Scale (SIS) – SIS Index, SIS-16 and SIS Visual Analogue Scale (SIS VAS); Work and Social Adjustment Scale (WSAS); and Barthel Index (BI). Quantile regression models were applied to investigate associations at the .25, median and .75 quantiles, with adjustments for covariates.

Results: The mean age of the cohort ($N = 219$) was 69 years ($SD = 13$), 140 (64%) were male and 154 (73%) had mild neurological deficits (NIHSS ≤ 6). Significant associations ($p \leq 0.005$) were demonstrated between MADRS and SIS Index, SIS-16, SIS VAS and WSAS scores, at 3 and 12 months post-stroke, except for SIS-16 at the .25 and median quantile at 3 months, and WSAS at the .25 quantile at 12 months. No significant associations were demonstrated between MADRS and BI scores, at any quantile, at either time point.

Conclusion: Depressive symptoms are associated with recovery outcomes, at 3 and 12 months post-stroke, as measured by SIS variants and WSAS, but not when measured by BI. Patient perceived outcome measures may have an advantage over observer-rated measures, in that they appear to better reflect the impact of depressive symptoms on recovery.

7.2 Introduction

Depression is widely recognised as a common consequence of stroke; approximately one-third of stroke survivors have depression, at any stage up to five years (Hackett & Pickles, 2014) and 10 years (Ayerbe, 2013a) post-stroke. Post-stroke depression is known to adversely impact stroke patients' motivation to participate in rehabilitation (Gillen et al., 2001). Further, post-stroke depression is associated with worse recovery outcomes, including: increased disability (Ayerbe et al., 2013a; Kutlubaev & Hackett, 2014); greater dependence in activities of daily living (Amaricai & Poenaru, 2016; Paolucci et al., 2019;); poorer functional recovery (Matsuzaki et al., 2015), reduced participation in work and social activities (Tse et al., 2017a; Tse et al., 2019); poorer quality of life (Kwok et al., 2006; Li et al., 2019) and increased risk of mortality (Cai et al., 2019; Ayerbe et al., 2013c).

Measuring 'recovery' is complex partly because the term implies capturing an assessment of 'overall recovery', which requires a synthesis of separate outcomes that reflect a range of deficits. This can be particularly challenging in stroke, compared to many other medical conditions, because stroke causes a wide range of residual disabilities (Adamson et al., 2004). Impairments such as paresis and aphasia are recognisable and can be assessed by widely used and established outcome measures. However, other sequelae of stroke such as cognitive impairment and depression may be more difficult to detect and measure in standard assessments – but can also impact functional status and quality of life (Rimmele et al., 2019). Further, recovery for stroke survivors depends on contextual factors including personal, environmental, and social resources (Vanhook, 2009).

Numerous outcome measures are used in stroke research and clinical practice to quantify recovery, monitor progress, and plan rehabilitation (Duncan, 2013a). These outcome measures differ in many ways, including in the specific constructs that each evaluates – even though all such constructs fall under the umbrella term 'recovery outcome'. Historically, recovery outcome measures have focused on domains such as physical function, disability and dependence (Mahoney & Barthel, 1965; Bonita & Beaglehole, 1988). More recently, outcome measures have been developed that also include domains relating to mood, cognition and social participation, such as the Stroke Impact Scale (SIS) (Duncan et al., 2003b) and the Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002). However, the association between post-stroke depressive symptoms and recovery, as evaluated by a range of outcome measures, has not yet been well characterised. Accordingly, the aim of this study was to explore the association between depressive symptoms and recovery over the first year following stroke, as evaluated across a profile of different, commonly used outcome measures.

7.3 Methods

7.3.1 Study Design

This cohort study of ischaemic stroke survivors was prospective, observational and longitudinal in design. Participants were recruited consecutively, via the Stroke Imaging Prevention and Treatment (START) collaborative research program, from 19 hospitals throughout Australia and New Zealand – all of which have specialised stroke units (Ma et al., 2012; Carey et al., 2015). Recruitment took place between June 2010 and April 2013; the study period was 12 months. Eligibility criteria required participants to be diagnosed with acute ischaemic stroke, to be 18 years or older, to be English-speaking, and to have no significant pre-stroke disability as determined by an estimated premorbid modified Rankin Scale (mRS) score ≤ 2 (Bonita & Beaglehole, 1998).

All participants were recruited as part of the START cohort via two study arms. Patients who were recruited 4.5 to 9 hours post-stroke, if they met additional inclusion criteria associated with suitability for thrombolysis, were enrolled in the Extending the Time for Thrombolysis in Emergency Neurological Deficits (START EXTEND) study arm (Ma et al., 2012). Patients recruited within 3 days following stroke, who met inclusion criteria, were enrolled in the Prediction and Prevention to Achieve Optimal Recovery Endpoints after stroke (START PrePARE) arm (Carey et al., 2015). Written informed consent was required of each participant, or their legally responsible person, prior to enrolment. The studies were approved at central hospital human research ethics committees, at each recruiting hospital site, and at tertiary institutions associated with the investigators.

Study participants were assessed at their recruiting hospital, or at their home, by a health professional trained in study procedures and administration of measures. At baseline, demographic and clinical characteristics of each participant were recorded, including age at stroke onset, sex and premorbid disability. At day 3 to 7 (± 1 day) post-stroke, stroke-related neurological deficits were evaluated using the National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989). At 3 months (± 7 days) and 12 months (± 7 days), depressive symptoms (the independent variable) and recovery outcomes (dependent variables) were measured.

7.3.2 Measures

Montgomery-Åsberg Depression Rating Scale (MADRS)

The Montgomery-Åsberg Depression Rating Scale (MADRS) was designed to assess the presence and severity of depressive symptoms (Montgomery & Åsberg, 1979). It was selected for use in this study because it is sensitive to change over time and has been shown to be more accurate than other measures that screen for post-stroke depression (Kang et al., 2013; Carey et al., 2015). MADRS items focus on core mood symptoms of depression as defined by the DSM, in contrast to

other screening tools that include items relating to somatic symptoms and motor retardation, which could be confounded by post-stroke impairments (Montgomery & Åsberg, 1979). The MADRS comprises ten items: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal ideation. Each item is scored from 0 to 6; the maximum possible total score is 60, with higher scores indicating more depressive symptoms (Montgomery & Åsberg, 1979).

We utilised the Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA) in the administration of the MADRS (Williams & Kobak, 2008). This interview guide asks the respondent about their mood over the preceding one week. Structured interview guides are increasingly used in the deployment of rating scales as they enable interviewers to score items more precisely. The MADRS SIGMA has been validated in stroke cohorts and has yielded high inter-rater reliability (intraclass correlation coefficient of 0.93) (Williams & Kobak, 2008). This was important in our study in order to standardise its use by multiple assessors, across multiple locations. A training video was developed by a neuropsychiatrist to further facilitate uniform administration of the MADRS SIGMA in this study.

Stroke Impact Scale (SIS)

The Stroke Impact Scale (SIS) version 3.0 is a patient-reported outcome measure which captures the impact of stroke across multiple dimensions (Duncan et al., 2003a). The SIS is a widely used, validated, reliable measure of patient functioning following stroke (Guidetti et al., 2014; Richardson et al., 2016). The SIS comprises 59 items across eight domains: strength (4 items), hand function (5 items), activities of daily living (10 items), mobility (9 items), communication (7 items), emotion (9 items), memory and thinking (7 items) and social participation (8 items). Each item asks the participant to score their perceived ability with a specific activity, over the previous two weeks; responses are scored on a 5-point scale from 1 (“could not do at all”) to 5 (“not difficult at all”). Each of the eight domain scores are considered separate, rather than added to yield an overall score (Duncan, 2003a). In this study, we used three variants of the SIS, each of which have been designed to yield a single overall score: the SIS Index, the SIS-16 and the SIS Visual Analogue Scale (SIS VAS).

SIS Index

The SIS Index measures patient perception of the overall impact of the stroke. The SIS Index was derived to yield a total ‘index score’ and has been validated among a cohort of stroke patients (Jenkinson et al., 2013). The index score is generated by summating all eight SIS domain scores and standardising this aggregate on a scale from 20 to 100 points; higher scores indicate lesser impact of stroke (Jenkinson et al., 2013).

SIS-16

The SIS-16 measures patient perception of stroke impact specifically on physical function. The SIS-16 was developed as an abridged version of the SIS using items only from physical function domains. It comprises 16 items across three domains: hand function (1 item), mobility (8 items) and activities of daily living (7 items). These 16 item scores are added and standardised on a scale from 20 to 100; higher scores correspond to lesser impact of stroke on physical functioning (Duncan, 2003b).

SIS Visual Analogue Scale (SIS VAS)

The SIS Visual Analogue Scale (SIS VAS) measures patient perception of global recovery after stroke and has demonstrated moderate correlation with a standardised measure of health-related quality of life in a stroke cohort (Richardson et al., 2015). It is a single question on the SIS independent of the eight domains. The SIS VAS asks the respondent to rate their global recovery post-stroke on a vertical visual analogue scale, from 0 signifying "no recovery" to 100 representing "full recovery" (Duncan, 2003a).

Work and Social Adjustment Scale (WSAS)

The Work and Social Adjustment Scale (WSAS) measures self-estimated work and social functioning (Mundt et al., 2002) and has been used in stroke cohorts (Tse et al., 2017b; Hommel et al., 2009). The WSAS asks respondents to estimate how much their activities and roles have been affected by the stroke, across five domains: work duties, home management, social leisure, private leisure, and close relationships. There is one question per domain and each response is rated on a 9-point scale from 0 ("no impairment") to 8 ("very severely impaired"). Scores obtained for each item are added to yield a total score ranging from 0 to 40 (Mundt et al., 2002). Higher scores indicate greater impairments when returning to previous activities and roles (Thandi et al., 2017).

Barthel Index (BI)

The Barthel Index (BI) measures functional independence in activities of daily living (Mahoney & Barthel, 1965) and is completed by observation and clinical judgement on the part of a clinician. The BI has been used extensively in both stroke research and clinical practice (Sangha et al., 2005; Quinn et al., 2011; Duncan, 2013). The BI comprises 10 items, each scored in increments of 5 points. Two items (bathing and personal hygiene) are rated on a 2-point scale (0 or 5); six items (feeding, dressing, bowel management, bladder management, accessing the toilet, and using stairs) are scored on a 3-point scale (0, 5 or 10); and the last two items (transferring and mobility) are recorded on a 4-point scale (0, 5, 10 or 15) (Mahoney & Barthel, 1965). For each item, a minimum score of 0 denotes inability to perform the activity independently, and the maximum

score indicates complete independence in that activity. Item scores are added to generate an overall score, which ranges from 0 ("complete functional dependence") to 100 ("complete independence") (Wallace et al., 2002; Uyttenboogart et al., 2007).

7.3.3 Statistical Analysis

Descriptive statistics were used to summarise demographic and clinical characteristics of the sample. Continuous data were expressed as: mean (*M*), standard deviation (*SD*), range, median (*Mdn*) and interquartile range (IQR). Categorical data were summarised as frequency (*n*) and percentage (%). Characteristics of included participants were compared with those non-included using Mann-Whitney U tests for continuous variables, and Pearson's Chi-square tests for categorical data.

Quantile regression models were applied to explore the association between depressive symptoms (MADRS) and recovery outcomes (SIS Index, SIS-16, SIS VAS, WSAS, BI) (Koenker & Bassett, 1978). Each regression model was fitted at the .25, median and .75 quantiles, at both the 3 month and 12 month time points. The use of quantile regression was supported by the presence of heteroscedasticity in the data (unequal variability across the dependent variable scales) (Breush & Pagan, 1979). The following factors, known to influence recovery after stroke, were adjusted for, in each model: age at stroke onset (Knoflach et al., 2012), sex of the stroke survivor (Bushnell et al., 2014), and neurological stroke severity, as measured by the NIHSS (Rost et al., 2016) at day 3 to 7 (± 1 day). The mean Variance Inflation Factor (VIF) and Condition Number (CN) were calculated to quantify the degree of multicollinearity between the independent variable (MADRS) and the covariates (age, sex and stroke severity). A mean VIF of 1.07 and CN of 14.28 at 3 months and a mean VIF of 1.05 and CN of 14.07 at 12 months were observed, indicating minimal multicollinearity in the models. Last, a multiplicity corrected *p* value was applied using the Bonferroni method. Accordingly, the level of statistical significance was set at $p \leq 0.005$, calculated by dividing the conventional significance level ($p \leq 0.05$) by the number of dependent variables analysed simultaneously (5 comparisons at 2 time points, $n = 10$). Statistical analyses were conducted using Stata version 16.1 (StataCorp, 2019).

7.4 Results

Participants from the START cohort ($N = 219$) were included in each analysis if they recorded both a MADRS score and the relevant outcome measure score, at each time point – and if their age, sex and NIHSS score were also recorded. Reasons for attrition between baseline and 3 months were withdrawal (2 participants), loss of contact (2 participants) and death (15 participants); 19 participants were recruited to replace these to meet the planned sample size of 200 at 3 months. Reasons for attrition between 3 months and 12 months were withdrawal (2 participants), loss of contact (8 participants) and death (6 participants).

7.4.1 Cohort characteristics (*N* = 219)

The START cohort comprised 219 ischaemic stroke patients. The mean age at stroke onset was 69 years (*SD* = 13) and 140 (64%) were male. The median NIHSS score, at day 3 to 7, was 3 (IQR = 6; Q1, Q3 = 1, 7); of the 210 participants with a recorded NIHSS score, 154 (73%) had mild neurological deficits (NIHSS score ≤ 6) (Rost, 2016). The median MADRS score at 3 months was 5 (IQR = 10; Q1, Q3 = 1, 11) and at 12 months was 4 (IQR = 10; Q1, Q3 = 0, 10) (Table 7.1).

Table 7.1

Cohort Characteristics (N = 219)

	N	***M* / %**	**SD**	**Range: min., max.**	***Mdn***	**IQR: Q1, Q3**
Age at stroke onset, years	219	69.07	13.07	27.47, 94.85	69.99	61.09, 79.62
Male sex	140	63.93%				
mRS, prior to stroke (0-6)	219					
0	187	85.39%				
1	31	14.16%				
2	1	0.46%				
NIHSS, day 3-7 (0-42) [a]	210	5.28	6.44	0, 32	3	1, 7
0-6 (mild)	154	73.33%				
7-16 (moderate)	36	17.14%				
17-40 (severe)	20	9.52%				
MADRS (0-60)						
3 months	178	7.40	7.56	0, 33	5	1, 11
12 months	165	6.45	6.79	0, 29	4	0, 10
SIS Index (20-100)						
3 months	185	80.87	20.65	12.61, 100	88.30	75.07, 95.39
12 months	169	83.20	21.14	0, 100	91.98	73.35, 97.33
SIS-16 (20-100)						
3 months	185	83.57	24.54	1.56, 100	95.31	78.13, 100
12 months	169	85.74	22.46	0, 100	95.31	79.69, 100
SIS VAS (0-100)						
3 months	180	73.63	23.98	0, 100	80	55, 92.5
12 months	169	78.10	23.05	0, 100	85	70, 95
WSAS (0-40)						
3 months	191	11.13	12.37	0, 40	7	0, 18
12 months	170	8.94	11.73	0, 40	3	0, 16
BI (0-100)						
3 months	196	85.26	28.85	0, 100	100	90, 100
12 months	184	88.61	25.13	0, 100	100	95, 100

Note. M = mean; *SD* = standard deviation; *Mdn* = median; IQR = interquartile range; Q1 = Quantile 1; Q3 = Quantile 3; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; SIS Index = Stroke Impact Scale Index; SIS-16 = Stroke Impact Scale Physical Functioning (16 items); SIS VAS = Stroke Impact Scale Visual Analogue Scale; WSAS = Work and Social Adjustment Scale; BI = Barthel Index.

[a] NIHSS score missing for 9 participants, *n* = 210.

7.4.2 Sample characteristics (*n* = 174)

At 3 months, sample sizes for each of the five analyses ranged from *n* = 168 to *n* = 175; at 12 months, sample sizes for each of the five analyses ranged from *n* = 154 to *n* = 162 (Table 7-S1, supplement). For the analysis that explored the association between MADRS and SIS Index at 3 months, the sample comprised 174 participants. Two of these participants were excluded from the analysis because they did not have an NIHSS score recorded at day 3 to 7. Of the 174 participants, the mean age at stroke onset was 67 (*SD* = 13) years and 114 (66%) were male. The median NIHSS score was 2 (IQR = 4.5; Q1, Q3 = 0, 4.5). Of the 172 participants with a recorded NIHSS score, 142 (83%) had mild neurological deficits (NIHSS score ≤ 6, day 3 to 7) (Rost et al., 2016). The median MADRS at 3 months was 5 (IQR = 10; Q1, Q3 = 1, 11). The median SIS Index at 3 months was 88 (IQR = 21; Q1, Q3 = 75, 96) (Table 7.2). Equivalent information for the other nine analyses are presented in Table 7-S1 (supplement).

Table 7.2

Sample Characteristics (n = 174)

	n	***M* / %**	***SD***	**Range: min., max.**	***Mdn***	**IQR: Q1, Q3**
Age at stroke onset, years	174	67.40	13.04	27.47, 90.99	68.33	60.40, 77.97
Male sex	114	65.52%				
mRS, prior to stroke (0-6)	174					
0	151	86.78%				
1	23	13.22%				
2	0	0%				
NIHSS, day 3-7 (0-42) [a]	172	3.89	5.29	0, 25	2	0, 4.5
0-6 (mild)	142	82.56%				
7-16 (moderate)	20	11.63%				
17-40 (severe)	10	5.81%				
MADRS (0-60)						
3 months	174	7.50	7.60	0, 31	5	1, 11
SIS Index (20-100)						
3 months	174	81.58	19.88	12.61, 100	88.41	75.31, 95.63

Note. M = mean; *SD* = standard deviation; *Mdn* = median; IQR = interquartile range; Q1 = quantile 1; Q3 = quantile 3; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; SIS Index = Stroke Impact Scale Index.
[a] NIHSS score missing for 2 participants.

7.4.3 Characteristics of included and non-included participants

Included participants had significantly milder neurological deficits (NIHSS, day 3 to 7) than non-included participants, in every sample ($p \leq 0.05$) and were significantly younger than those non-included ($p \leq 0.05$) in all but one analysis. There were no significant differences between included and non-included participants in relation to premorbid disability (mRS) and sex of the individual ($p > 0.05$) (Table 7-S1, supplement).

7.4.4 Associations between Depressive Symptoms and Recovery Outcomes at 3 and 12 Months

Using the multiplicity corrected significance level ($p \leq 0.005$), quantile regression models yielded the following associations between MADRS scores and the five recovery outcome measure scores (SIS Index, SIS-16, SIS VAS, WSAS, and BI) at 3 and 12 months (Table 7.3).

Associations between MADRS and SIS Index

At both time points, quantile regression models yielded significant negative associations between MADRS and SIS Index scores, at all quantiles, after adjustment for age, sex and stroke severity. This demonstrates that more severe depressive symptoms (higher scores on the MADRS) were associated with poorer perceived impact of stroke (lower scores on the SIS Index). At 3 months (n = 172), a one-point increase in MADRS score was associated with a 1.19-point decrease in SIS Index score, at the .25 quantile (95% CI [-1.58, -0.81]; $p < 0.001$), a 0.87-point decrease at the median (95% CI [-1.11, -0.63]; $p < 0.001$) and a 0.71-point decrease at the .75 quantile (95% CI [-0.96, -0.46]; $p < 0.001$). At 12 months (n = 154), a one-point increase in MADRS score was associated with a 1.49-point decrease in SIS Index score, at the .25 quantile (95% CI [-1.80, -1.17]; $p < 0.001$), a 0.85-point decrease at the median (95% CI [-1.13, -0.58]; $p < 0.001$) and a 0.69-point decrease at the .75 quantile (95% CI [-0.88, -0.50]; $p < 0.001$).

Associations between MADRS and SIS-16

At 3 months, quantile regression models yielded significant negative associations between MADRS and SIS-16 scores at the median quantile, following adjustment for covariates. At 3 months (n = 172), a one-point increase in MADRS score was associated with a 0.74-point decrease in SIS-16 score, at the median (95% CI [-1.10, -0.38]; $p < 0.001$). At 12 months (n = 155), a one-point increase in MADRS score was associated with a 1.03-point decrease in SIS-16 score, at the .25 quantile (95% CI [-1.64, -0.41]; $p = 0.001$), a 0.66-point decrease at the median (95% CI [- 0.94, -0.37]; $p < 0.001$) and a 0.37-point decrease at the .75 quantile (95% CI [-0.61, -0.14]; $p = 0.002$).

Associations between MADRS and SIS VAS

At both time points, quantile regression models yielded significant negative associations between MADRS and SIS VAS scores, at all quantiles, after adjustment for covariates. At 3 months (n = 168), a one-point increase in MADRS score was associated with a 1.03-point decrease in SIS VAS score, at the .25 quantile (95% CI [-1.74, -0.33] $p = 0.004$), a 0.94-point decrease at the median (95% CI [-1.43, -0.44]; $p < 0.001$) and a 0.83-point decrease at the .75 quantile (95% CI [-1.16, -0.50; $p < 0.001$). At 12 months (n = 155), a one-point increase in MADRS score was associated with a 1.06-point decrease in SIS VAS score, at the .25 quantile (95% CI [-1.53, -

0.59]; $p < 0.001$), a 0.88-point decrease at the median (95% CI [-1.38, -0.38]; $p = 0.001$) and a 0.55-point decrease at the .75 quantile (95% CI [-0.83, -0.27]; $p < 0.001$).

Associations between MADRS and WSAS

Except for the .25 quantile at 12 months, quantile regression models yielded significant positive associations between MADRS and WSAS scores, for all other quantiles, following adjustment for covariates. At 3 months ($n = 173$), a one-point increase in MADRS score was associated with a 0.38-point increase in WSAS score, at the .25 quantile (95% CI [0.20, 0.55]; $p < 0.001$), a 0.53-point increase at the median (95% CI [0.32, 0.73] $p < 0.001$) and a 0.83-point increase at the .75 quantile (95% CI [0.57, 1.09]; $p < 0.001$). At 12 months ($n = 156$), a one-point increase in MADRS score was associated with a 0.54-point increase in WSAS score, at the median (95% CI [0.32, 0.76]; $p < 0.001$) and a 0.92-point increase at the .75 quantile (95% CI [0.66, 1.18]; $p < 0.001$).

Associations between MADRS and BI

The quantile regression models did not demonstrate any statistically significant associations between MADRS and BI scores, at any quantile, at either 3 or 12 months after stroke.

Table 7.3

Associations between Depressive Symptoms and Recovery Outcomes at 3 and 12 Months

	3 months			12 months		
		MADRS			MADRS	
	n	Coefficient (95% CI)	*p*	*n*	Coefficient (95% CI)	*p*
SIS Index						
.25 quantile		-1.19 (-1.58, -0.81)	**<0.001**		-1.49 (-1.80, -1.17)	**<0.001**
median	172 [a]	-0.87 (-1.11, -0.63)	**<0.001**	154 [b]	-0.85 (-1.13, -0.58)	**<0.001**
.75 quantile		-0.71 (-0.96, -0.46)	**<0.001**		-0.69 (-0.88, -0.50)	**<0.001**
SIS-16						
.25 quantile		-0.61 (-1.15, -0.08)	0.023		-1.03 (-1.64, -0.41)	**0.001**
median	172 [a]	-0.74 (-1.10, -0.38)	**<0.001**	155 [b]	-0.66 (-0.94, -0.37)	**<0.001**
.75 quantile		-0.35 (-0.61, -0.10)	0.007		-0.37 (-0.61, -0.14)	**0.002**
SIS VAS						
.25 quantile		-1.03 (-1.74, -0.33)	**0.004**		-1.06 (-1.53, -0.59)	**<0.001**
median	168 [a]	-0.94 (-1.43, -0.44)	**<0.001**	155 [b]	-0.88 (-1.38, -0.38)	**0.001**
.75 quantile		-0.83 (-1.16, -0.50)	**<0.001**		-0.55 (-0.83, -0.27)	**<0.001**
WSAS						
.25 quantile		0.38 (0.20, 0.55)	**<0.001**		0.22 (0.00, 0.45)	0.046
median	173 [a]	0.53 (0.32, 0.73)	**<0.001**	156 [b]	0.54 (0.32, 0.76)	**<0.001**
.75 quantile		0.83 (0.57, 1.09)	**<0.001**		0.92 (0.66, 1.18)	**<0.001**
BI						
.25 quantile		-0.43 (-0.90, 0.03)	0.069		-0.17 (-0.59, 0.25)	0.424
median	175 [a]	-0.29 (-0.63, 0.04)	0.088	162 [b]	-0.15 (-0.52, 0.21)	0.408
.75 quantile		0.00 (-0.15, 0.15)	1.000		0.00 (-0.06, 0.06)	1.000

Note. [a] NIHSS score missing for 2 participants (therefore not included in the analysis); [b] NIHSS score missing for 1 participant (therefore not included in the analysis).
p values recorded in boldface indicate significance based on the multiplicity corrected *p* value ($p \leq 0.005$).

7.5 Discussion

In this cohort of ischaemic stroke patients, we have demonstrated independent associations between depressive symptoms and recovery outcomes, as measured by SIS Index, SIS-16, SIS VAS and WSAS, at both 3 and 12 months following stroke. The associations were statistically significant at all quantiles except for three (.25 quantile and .75 quantile for SIS-16 at 3 months, and .25 quantile for WSAS at 12 months) – even with the conservative application of the multiplicity corrected significance level ($p \leq 0.005$). In contrast, the association between depressive symptoms and recovery outcome as measured by the BI was not statistically significant, at any quantile, at either time point.

One possible explanation for this observed discrepancy between the associations of depressive symptoms and recovery, as assessed by the outcome measures studied, may be related to the source of responses collected to complete the items in each outcome measure. The SIS Index, SIS-16, SIS VAS and WSAS collect data provided directly by the participant. Such patient-reported outcome measures capture the individual's own perspective, without external influence

or interpretation (Reeves et al., 2018). Patient-reported outcome measures provide useful information about the expectations, needs and values that are most meaningful to the patient (Ytterberg et al., 2017). These measures may better reflect the impact of residual deficits that can occur following stroke, such as depression.

In contrast, the BI is an observer-rated outcome measure that involves the collection of information by an independent assessor, by observation of the patient and by clinical judgement (Reeves et al., 2018). Such measures are long established and widely used in both stroke research and clinical practice. They provide useful, objective information that is considered to be precise – however, they may not fully reflect an individual's perception of the impact of the stroke on their quality of life.

Patient-reported outcome measures, however, are not without their own inherent disadvantages (Stewart & Cramer, 2013). By their nature, such measures are subjective and rely on participants' self-appraisal, which may be erroneous or prone to inconsistencies (Reeves et al., 2018). Further, these measures can be difficult to deploy in the context of common post-stroke sequelae, such as communication impairments, cognitive deficits and severe fatigue (Barrett, 2010; Stewart & Cramer, 2013; Katzan et al., 2017). Another disadvantage of patient-reported outcome measures is that the time required for their administration may be longer than that for observer-rated outcome measures, particularly when the instrument comprises numerous items. Their use may increase both patient and assessor burden (Price-Haywood et al., 2009).

Despite these potential disadvantages, our findings appear to show that the four patient-reported outcome measures used in this study enabled stroke survivors with depressive symptoms to express, in some way, the impact of these symptoms on their recovery following stroke. In the case of the SIS Index, the impact of depressive symptoms is expressed directly via the emotion domain. For the SIS-16 and SIS VAS, although these measures do not include items specifically evaluating the construct of mood, the impact of depressive symptoms could still be reflected indirectly by more negative responses in other items. Regarding the WSAS, the impact of depressive symptoms may be expressed indirectly via the related construct of participation in premorbid work roles and social activities. The association between participation and depressive symptoms has already been established at three months, one year and five years post-stroke (Tse et al., 2017a; Tse et al., 2019; Palstam et al., 2019).

In the context of our findings, it may be informative to compare the BI with the SIS-16, because both measures evaluate the constructs of physical functioning and performance in activities of daily living. The BI, however, is known to have a marked ceiling effect – the phenomenon in which high scores are sometimes generated despite the presence of substantial deficits (Kwon et

al., 2004; Quinn et al., 2011). This likely limits its utility because it is less able to discriminate between patients with mild functional impairments (Quinn et al., 2011). For example, a BI score of 95 or 100 indicates minimal or no disability – but the overall impact of stroke may be underestimated (Lai et al., 2002b). The SIS-16 was developed in order to assess physical impairments beyond those which could be measured by the BI (Duncan et al., 2003c). It includes items that refer to more complex activities of daily living, such as vacuuming, washing clothes, walking quickly or walking moderate distances. The SIS-16 can better differentiate between stroke survivors with mild functional impairments and therefore is less susceptible to a ceiling effect (Duncan et al., 2003c). A key difference between the two measures is that the SIS-16 is a patient-reported outcome measure, whereas the BI is an observer-rated outcome measure. Neither measure includes items directly relating to the constructs of mood, nor even to participation. However, the SIS-16 appears to allow respondents to express the impact of depressive symptoms indirectly via their responses to the physical functioning items. This may account, at least in part, for our finding that recovery of physical function, as measured by the SIS-16, was significantly associated with depressive symptoms, in contrast to the BI.

However, it may be that the lack of significant associations between the MADRS and BI, rather than being due to the observer-rated characteristic of the instrument, was due to the predominantly milder neurological severity in this particular cohort. At least half of all participants scored at the ceiling level of 100 on the BI, at both 3 and 12 months. This reflects that many stroke survivors appear to have regained functional independence in activities of daily living. This may have obscured any underlying significant association between scores on the BI and MADRS.

There are some limitations to this study. Despite efforts to support the inclusion of patients with severe neurological impairments, the majority of participants in the samples had an NIHSS score ≤ 6 at day 3 to 7, indicating mild neurological deficits (Rost et al., 2016). The proportions of 'mild' stroke across each of the ten samples ranged from 82 to 85 per cent. Further, each sample had a lower mean age at stroke (ranging from 67 to 68 years) compared with the mean age for national figures (73 years) reported by the Australian Stroke Clinical Registry (AuSCR) (Breen et al., 2020). Each sample had a lower proportion of females (ranging from 33% to 34%) compared with the proportion of females (45%) reported by AuSCR (Breen et al., 2020). All participants in this study had ischaemic stroke, whereas 70 per cent of national registry patients had ischaemic stroke (Breen et al., 2020).

Next, although we controlled for covariates known to influence recovery (age, sex and neurological severity), there may be other factors that also influence the association between depressive symptoms and recovery. For example, post-stroke fatigue, anxiety, cognitive impairment and language deficits, some of which may be quite subtle, could coexist with

depressive symptoms and may also influence recovery (Patchick et al., 2015). Further, this study does not report, nor adjust for, participants who previously had depression, or who received treatment for depression during the study.

Finally, a limitation is that only one observer-rated outcome measure was used in the analysis, the BI. The modified Rankin Scale (mRS) is another observer-rated, functional outcome measure, commonly used by stroke clinicians and researchers (Bonita & Beaglehole, 1988). We considered including the mRS as a sixth outcome measure in this study. However, the mRS generates scores on an ordinal scale, which includes only six ordered grades of functional outcome and a death state (Rethnam et al., 2021). Accordingly, mRS scores are treated as ordinal data and are not suitable for the method of analysis used in this paper. We recommend that the association between depressive symptoms and outcomes, as measured by the mRS, be explored in future research.

Based on these findings, we recommend the routine use of patient-reported recovery outcome measures, alongside observer-rated measures, in stroke rehabilitation. Understanding the impact of the stroke from the perspective of the patient facilitates collaborative decision making and promotes patient-centred care (Ytterberg et al., 2017; Katzan et al., 2017). Stroke survivors who are active participants in their own rehabilitation are more likely to improve in their recovery (Ytterberg et al., 2017). Further, we suggest the inclusion of patient-reported outcomes in future research to obtain a more complete understanding of the impact of post-stroke depression on recovery.

7.6 Conclusion

In this study, we have demonstrated significant, independent associations between depressive symptoms and recovery outcomes, as measured by the SIS Index, SIS-16, SIS VAS and WSAS, at 3 months and 12 months following stroke. In contrast, no significant association between depressive symptoms and recovery outcome as measured by the BI was observed, at either time point. Patient-reported outcome measures appear to better reflect the impact of post-stroke depressive symptoms – thus providing important insights into a stroke survivor's perception of their recovery.

Supplementary Material

Table 7-S1. *Demographic and Clinical Characteristics of Included and Non-Included Participants for Each Model*

		3 months			12 months		
		Included	**Non-Included**	***p***	**Included**	**Non-Included**	***p***
MADRS & SIS Index	*n*	174	45		155	64	
	age at stroke onset, mean (*SD*)	67.40 (13.04)	75.56 (11.10)	**<0.001**	67.57 (13.07)	72.71 (12.41)	**0.014**
	sex: male	114	26	0.335	103	37	0.226
	no pre-stroke disability: mRS score=0, frequency	151	36	0.186	136	51	0.128
	neurological deficit, day 3 to 7 (NIHSS, 0-42), median [Q1; Q2]	2 [0; 4.5][a]	11.5 [5; 17][b]	**<0.001**	2 [0; 4][c]	10 [4; 16][d]	**<0.001**
MADRS & SIS-16	*n*	174	45		156	63	
	age at stroke onset, mean (*SD*)	67.40 (13.04)	75.56 (11.10)	**<0.001**	67.54 (13.04)	72.88 (12.44)	**0.010**
	sex: male, frequency	114	26	0.335	104	36	0.184
	no pre-stroke disability: mRS score=0, frequency	151	36	0.101	137	50	0.114
	neurological deficit, day 3 to 7 (NIHSS, 0-42), median [Q1; Q2]	2 [0; 4.5][a]	11.5 [5; 17][b]	**<0.001**	2 [0; 4][c]	10 [4; 16][d]	**<0.001**
MADRS & SIS VAS	*n*	170	49		156	63	
	age at stroke onset, mean (*SD*)	67.14 (12.99)	75.78 (11.06)	**<0.001**	67.54 (13.04)	72.88 (12.44)	**0.010**
	sex: male, frequency	113	27	0.144	104	36	0.184
	no pre-stroke disability: mRS score=0	148	39	0.105	137	50	0.114
	neurological deficit, day 3 to 7 (NIHSS, 0-42), median [Q1; Q2]	2 [0; 4][a]	13 [5; 17][b]	**<0.001**	2 [0; 4][c]	10 [4;16][d]	**<0.001**
MADRS & WSAS	*n*	175	44		157	62	
	age at stroke onset, mean (*SD*)	67.30 (13.07)	76.13 (10.54)	**<0.001**	67.56 (13.06)	72.90 (12.38)	**0.010**
	sex: male, frequency	115	25	0.272	105	35	0.148
	no pre-stroke disability: mRS score=0, frequency	152	35	0.089	138	49	0.101
	neurological deficit, day 3 to 7 (NIHSS, 0-42), median [Q1; Q2]	2 [0; 4][a]	12 [6; 17][b]	**<0.001**	2 [2; 4.5][c]	9.5 [3; 15][d]	<0.001
MADRS & BI	*n*	177	42		163	56	
	age at stroke onset, mean (*SD*)	67.50 (13.12)	75.72 (10.61)	**0.003**	68.01 (13.12)	72.15 (12.54)	0.065
	sex: male, frequency	116	24	0.308	108	32	0.220
	no pre-stroke disability: mRS score=0, frequency	154	33	0.068	142	45	0.338
	neurological deficit, day 3 to 7 (NIHSS, 0-42), median [Q1; Q2]	2 [0; 5][a]	12 [6; 17][b]	**<0.001**	2 [0; 5][c]	9.5 [4; 15][d]	**<0.001**

Note. Included participants were compared with those non-included using the Mann-Whitney U test for continuous variables and Pearson's Chi-square test for categorical data.
SD = standard deviation; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale.
[a] NIHSS score missing for 2 participants; [b] NIHSS score missing for 7 participants; [c] NIHSS score missing for 1 participant; [d] NIHSS score missing for 8 participants.
Statistically significant results ($p \leq 0.05$) are recorded in boldface.

Chapter 8.

Empirical Study 3: Comorbidity Burden and Perceived Recovery

Introduction to chapter

The findings of the preceding chapter (Empirical Research Study 2) highlighted the value of patient-reported outcome measures in detecting the impact of depressive symptoms on overall recovery post-stroke. This generated interest in further exploring the notion of patient perceived recovery in stroke populations. In particular, the question was raised of whether associations could be detected between patients' pre-stroke health status and post-stroke recovery, as evaluated by patient-reported outcome measures.

Comorbidity burden is a marker of health experience, and the presence of comorbidities can compromise recovery following stroke. A high prevalence of comorbidities exists among stroke survivors (Corraini et al., 2018); stroke without comorbidities occurs in less than six per cent of the stroke population (Guthrie et al., 2012). It has been demonstrated that stroke patients with a higher number of pre-existing comorbidities prior to admission for stroke, were more likely to report being moderately or severely depressed after the stroke, compared to those with lesser comorbidity burden (Thayabaranthan et al., 2018). Previous literature has demonstrated associations between comorbidity burden and post-stroke outcomes using observer-rated measures of function, disability and dependence (Carod-Artal & Egido, 2009).

The research question for Empirical Research Study 3 is: What is the association between comorbidity burden and patient perceived recovery within the first year post-stroke?

Pre-existing Comorbidity Burden and Patient Perceived Stroke Impact

Authors: Katherine Sewell, MPH[1,2], Tamara Tse, PhD[1,3], Elizabeth Harris, PHD[1,2], Thomas Matyas, PhD[1,2], Leonid Churilov, PhD[4], Henry Ma, PhD[5], Stephen M. Davis, MD[6], Geoffrey A. Donnan, MD[6] and Leeanne M. Carey, PhD[1,2] .

Affiliations:

1. Department of Occupational Therapy, Social Work and Social Policy, School of Allied Health, Human Services and Sport, La Trobe University, Bundoora, Australia
2. Neurorehabilitation and Recovery, Florey Institute of Neuroscience and Mental Health, Heidelberg, Australia
3. Department of Occupational Therapy, St Vincent's Hospital Melbourne, Fitzroy, Australia
4. Melbourne Medical School, University of Melbourne, Melbourne, Australia
5. Department of Medicine, School of Clinical Sciences, Monash University, Melbourne, Australia
6. Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia

Contributions of authors: KS contributed to the conceptualisation, design and methodology of the study; performed the statistical analysis and wrote the manuscript. LMC was the principal investigator for the cohort study in the START research program. LMC and TT contributed to the study design and methodology, and the writing, reviewing and editing of the manuscript. EH and LC contributed to the development of the statistical methodology and the analysis of the data; verified the interpretation of the results; and provided revision of the manuscript. HM, SD, GD reviewed iterations of the manuscripts and provided substantive feedback. All authors contributed to the final manuscript.

Publication status: Published in International Journal of Stroke (IJS). Received 24 September 2019; accepted 26 January 2020; published online 13 April 2021.

Citation: 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

Permission: SAGE's Author Archiving and Re-Use Guidelines state "the Final Published PDF (or Original Submission or Accepted Manuscript, if preferred) [may be used] in … your dissertation or thesis, including where the dissertation or thesis will be posted in any electronic Institutional Repository or database". This information was accessed SAGE Publications (2021) from: https://au.sagepub.com/en-gb/oce/journal-author-archiving-policies-and-re-use, 23 August 2021 (Appendix S).

Format: This study has been formatted consistently in the style of this thesis, independent of the style required by IJS. Tables are included in the body of the manuscript and the supplementary material is presented at the end of this study and chapter. All in-text citations of this study are recorded in the single reference list at the end of this thesis.

Authors' note: We acknowledge that the scoring of the Charlson Comorbidity Index (CCI) – and in particular, the inclusion or exclusion of the index morbidity (in this case, 'cerebrovascular disease') varies across related literature. The intention of the use of the CCI – as measure of comorbidity burden – was to capture the impact of all health conditions experienced by an individual, at the time of the assessment. Therefore, the START research team decided to assign a score of '1' for the presence of 'cerebrovascular disease' on the CCI, for each participant. We acknowledge that this one point given to each participant for the presence of stroke could have been omitted from their overall CCI score.

8.1 Abstract

Background: Pre-existing comorbidities can compromise recovery post-stroke. However, the association between comorbidity burden and patient-rated perceived impact has not been systematically investigated. To date, only observer-rated outcome measures of function, disability and dependence have been used, despite the complexity of the impact of stroke on an individual.

Aim: Our aim was to explore the association between comorbidity burden and patient-rated perceived impact and overall recovery, within the first-year post-stroke, after adjusting for stroke severity, age and sex.

Methods: The sample comprised 177 stroke survivors from 18 hospitals throughout Australia and New Zealand. Comorbidity burden was calculated using the Charlson Comorbidity Index (CCI). Perceived impact and recovery were measured by the Stroke Impact Scale (SIS) index and SIS overall recovery scale. Quantile regression models were applied to investigate the association between comorbidity burden and perceived impact and recovery.

Results: Significant negative associations between the CCI and the SIS index were found at 3 months. At the .25 quantile, a one-point increase on the CCI was associated with 6.80-points decrease on the SIS index (95% CI [-11.26, -2.34]; $p = 0.003$). At the median and .75 quantile, a one-point increase on the CCI was associated, respectively, with 3.58-points decrease (95% CI [-5.62, -1.54]; $p = 0.001$) and 1.76-points decrease (95% CI [-2.80, -0.73]; $p = 0.001$), on the SIS index. At 12 months, at the .25 and .75 quantiles, a one-point increase on the CCI was associated, respectively, with 6.47-points decrease (95% CI [-11.05, -1.89]; $p = 0.006$) and 1.26-points decrease (95% CI [-2.11, -0.42]; $p = 0.004$) on the SIS index. For the SIS overall recovery measure, significant negative associations were found only at the median at 3 months, and at the .75 quantile at 12 months.

Conclusion: Comorbidity burden is independently associated with patient-rated perceived impact within the first year post-stroke. The addition of patient-rated impact measures in personalised rehabilitation may enhance the use of conventional observer-rated outcome measures.

8.2 Introduction

The presence of comorbidities, particularly when numerous or severe, can compromise recovery outcomes post-stroke. Comorbidities have been shown to be associated with higher mortality rates (Goldstein et al., 2004; Bar & Hemphill, 2011; Guthrie et al., 2012; Jiménez Caballero et al., 2013; Corraini et al., 2018) longer lengths of stay in hospital (Lim, 2015), increased re-hospitalisation rates (Berlowitz et al., 2008), reduced function (Berlowitz et al., 2008; Turhan et al., 2009), and greater disability and dependence (Goldstein et al., 2004; Bar et al., 2011; Jiménez Caballero et al., 2013). A high prevalence of comorbidities exists among stroke survivors (Corraini et al., 2018); stroke without comorbidities occurs in less than six per cent of the stroke population (Guthrie et al., 2012). The association between comorbidity burden and stroke outcomes has been studied using independently observed measures of function, disability and dependence (Carod-Artal & Egido, 2009). This association, for example, has been demonstrated using the Functional Independence Measure (Keith et al., 1987) at discharge (Turhan et al., 2009) and six-months post-stroke (Berlowitz et al., 2008), and the modified Rankin Scale (mRS) (Farrell et al., 1991) at discharge (Goldstein et al., 2004), six-months (Jiménez Caballero et al., 2013) and one-year (Bar & Hemphill, 2011) post-stroke. However, the association between comorbidity burden and stroke impact and recovery – as perceived by the stroke survivor – has not yet been systematically explored.

The notion of patient-rated perceived recovery refers to an individual's own experience and assessment of the impact of the stroke on their level of function and general health. Patient-rated perceived recovery and impact are important to consider, in addition to conventional observer-rated measures of recovery, because in patient-perceived evaluations, the patient can account for, and synthesise, a range and complexity of factors they believe are important to their recovery. These factors include the individual's particular circumstances and psychosocial factors, such as: sense of stroke impact on prior health status; sense of loss relating to the effect of stroke on premorbid roles and responsibilities; hope and expectation for good recovery; worry and fear of poor recovery; prior experience and resilience to adverse events; ability to accept and adjust to impairment; availability of family and community supports; self-esteem and confidence in social situations; and motivation to engage in rehabilitation. Understanding the perceived stroke impact on an individual, in addition to undertaking independently observed measures, aligns with a patient-centred approach and should enable the refinement of treatment plans to better meet individual needs (Ytterberg et al., 2017). The degree of perceived recovery and impact may differ from observer-rated scores generated by conventional measures of function, disability and dependence (Snögren & Sunnerhagen, 2009).

The aim of this study was to explore the association between comorbidity burden and patient-rated perceived stroke impact and recovery, within the first-year post-stroke, after adjusting for

factors known to influence recovery outcomes – age at stroke onset (Knoflach et al., 2012), sex of the stroke survivor (Bushnell et al., 2014) and stroke severity (Rost et al., 2016).

8.3 Methods

8.3.1 Study design

This study was a prospective, observational, longitudinal cohort design comprising 219 ischaemic stroke survivors. Participants were recruited via the Stroke Imaging Prevention and Treatment (START) collaborative research program which comprised two arms: the Prediction and Prevention to Achieve Optimal Recovery Endpoints after stroke (START PrePARE) cohort – for participants recruited within three days post-stroke (Carey et al., 2015); and the Extending the Time for Thrombolysis in Emergency Neurological Deficits (START EXTEND) cohort – for those recruited between 4.5 and 9 hours post-stroke (Ma et al., 2012).

8.3.2 Participants and centres

Eligibility for the START program required participants to be diagnosed with ischaemic stroke, be at least 18 years of age, be proficient in the English language and have no premorbid significant disability, as determined by a score of less than three on the mRS. Additional inclusion criteria associated with eligibility for the thrombolysis with tissue Plasminogen-Activator (tPA) were required for participants recruited via the START EXTEND study (Ma et al., 2012). Between June 2010 and April 2013, at hospitals throughout Australia and New Zealand – all of which had specialised stroke units – all eligible, consecutive patients presenting with ischaemic stroke were invited to take part in the study. Informed consent for participation, prior to the commencement of data collection, was obtained from the patient, or their family member or legally responsible person. Following recruitment, all participants were contacted again, at each assessment time point, and invited to continue participating in the study. The study was approved by the ethics committees responsible for each recruiting hospital site and the tertiary institution involved.

8.3.3 Measures

Standardised assessments were undertaken by health professionals trained in the conduct of the measures, between 3 and 7 days (±1 day), at 3 and 12 months (±7 days) post-stroke, at hospital recruitment sites or in participants' homes. Demographic data, including the participant's age at stroke onset and sex, was collected on admission. Stroke severity was measured by the National Institutes of Health Stroke Scale (NIHSS) between 3 and 7 days (±1 day) following stroke onset. The NIHSS assesses neurological status post-stroke and correlates highly with stroke severity (Brott et al., 1989). Scores on the NIHSS range from 0 to 42; low scores indicate mild severity, and higher scores denote greater neurological deficit.

Comorbidity burden was estimated by the Charlson Comorbidity Index (CCI) and calculated retrospectively from questionnaires, and patient or proxy reports collected on admission. The index has been validated to predict functional outcome within the stroke population (Tessier et al., 2008). The CCI was scored by assigning a value of 1, 2, 3 or 6 to each medical condition, based on its one-year mortality risk, that antedated the onset of the stroke (Charlson et al., 1987). In this study, all participants received a score of at least 1 for the presence of cerebrovascular disease. The score for each existing condition was summated to yield a total score for each participant, reflecting their cumulative burden of comorbidities – with higher scores indicating greater comorbidity burden (Fischer et al., 2006) (Table 8-S1, supplement).

Patient-rated perceived impact of stroke and overall recovery were determined using the Stroke Impact Scale (SIS) version 3.0 (Duncan et al., 2003a) at 3 and 12 months post-stroke. The SIS comprises 59 items across eight domains: strength, memory, emotion, communication, activities of daily living, mobility, hand function and social participation. Perceived impact of stroke was measured by the SIS index; this was generated by aggregating each domain score and standardising the total on a 100-point scale, with higher scores indicating less perceived stroke impact. The SIS index has been validated among a cohort of stroke patients (Jenkinson et al., 2013). Patient-rated perceived overall recovery was measured by the final item on the SIS, independent of the eight domains. This item, referred to as 'SIS overall recovery' hereafter, asks the respondent to provide a single score on a visual analogue scale from 0 to 100, representing their perceived global recovery, with higher scores signifying a better perceived overall recovery (Carod-Artal et al., 2008)

8.3.4 Data analysis

Statistical analyses were conducted using Stata 14.0 (StataCorp, 2015). A large portion of cases with high scores recorded in both outcome measures was observed; the Breusch-Pagan test (Breusch & Pagan, 1979) confirmed the presence of heteroscedasticity in the data ($p = 0.005$). Therefore, quantile regression models were applied, in lieu of parametric regression models, to investigate the association between the CCI scores and the SIS index and overall recovery scores. Quantile regression provides a comprehensive statistical representation of the association across the distribution of the outcome variable (Koenker & Bassett, 1978); for each SIS measure, regression models were fitted at the .25, median and .75 quantiles, for both time points. The covariates, age, sex and baseline stroke severity, were adjusted for in each regression model. The Variance Inflation Factor (VIF) and Condition Index (CI) were used to detect multicollinearity; a mean VIF of 1.10 and CI of 15.23 were observed, indicating a low degree of interaction between the covariates. Lastly, a Bonferroni correction ($\alpha = 0.025$) was undertaken because two regression analyses were applied to the dataset.

8.4 Results

8.4.1 Participant flow

From the initial START cohort of 219, participants were excluded from this analysis if no CCI nor NIHSS scores had been documented (9 exclusions). At 3 months, participants were excluded, respectively, from each of the two arms of the analysis if: (a) no SIS index had been recorded (33 exclusions); or (b) no SIS overall recovery scale had been recorded (37 exclusions). These criteria yielded, for this time point, 177 inclusions in the SIS index analysis and 173 inclusions in the SIS overall recovery scale analysis. At 12 months, remaining participants were excluded, respectively, from each of the two arms of the analysis if: (a) no SIS index had been recorded (21 exclusions); or (b) no SIS overall recovery scale had been recorded (17 exclusions). This yielded 156 inclusions in each of the 12 month analyses. Reasons for attrition from baseline included: inability to contact the participant, participant withdrawal and participant death.

8.4.2 Demographic and clinical characteristics

At 3 months, the study sample comprised 177 stroke survivors; 119 (67%) were male and the sample mean age at stroke onset was 68 (*SD* = 13) years. There was a median CCI score of 3 (IQR = 2) and a median NIHSS score of 3 (IQR = 7), indicating primarily mild neurological Severity. A total of 36 (31%) participants had received thrombolysis with tPA, either as part of the START EXTEND (Ma et al., 2012) study, or as part of clinical care in the START PrePARE (Carey et al., 2015) cohort study (Table 8.1).

Table 8.1

Demographic and Clinical Characteristics of Included and Excluded Participant Groups for SIS Index Analysis at 3 Months

	Included participants (*n* = 177)				**Excluded participants (*n* = 42)**				
	n	*M* (*SD*)	range	*Mdn* (IQR)	*n*	*M* (SD)	range	*Mdn* (IQR)	*p*
Age at stroke, years	177	68 (13)	28, 91	69 (17)	42	73 (13)	42, 95	76 (20)	**0.029**
Sex									0.037
male	119				21				
female	58				21				
Comorbidity burden, CCI (0-35)	177	2.73 (1.41)	1, 8	3 (2)	42	3.43 (1.23)	1, 6	3 (2)	**0.002**
Stroke severity at day 3 to 7, NIHSS (0-42)	177	5.28 (6.32)	0, 32	3 (7)	35	10.34 (8.17)	0, 32	11 (14)	**0.001**
Thrombolysis with tPA	36				13				0.138

Note. M = mean; *SD* = standard deviation; *Mdn* = median; IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale. tPA = tissue Plasminogen-Activator.
Significant *p* values in boldface.

Mann Whitney U tests indicated a statistically significant difference between participants included (n = 177) and those excluded (n = 42) in regard to their age at stroke (p = 0.029), comorbidity burden (p = 0.002) and stroke severity (p = 0.001). Chi-Square tests demonstrated a significant group Difference relative to the sex of the individual (p = 0.037); however, in relation to administration of tPA, there was no significant difference (p = 0.138) (Table 8-S1, supplement). Descriptive statistics, including measures of central tendencies, were calculated for the outcome measures at both time points (Table 8.2).

Table 8.2.

Descriptive Statistics for SIS Index and SIS Overall Recovery Scale

	n	***M* (*SD*)**	**Range (min., max)**	***Mdn* (IQR)**
SIS Index (0-100)				
3 months	177	80.70 (20.99)	12.61, 100	88.36 (20.32)
12 months	156	83.71 (20.35)	0, 100	92.04 (24.83)
SIS VAS (0-100)				
3 months	173	74.09 (23.64)	0, 100	80 (40)
12 months	156	78.65 (22.06)	0, 100	85 (25)

Note. M = mean; *SD* = standard deviation; *Mdn* = median; IQR = interquartile range.

8.4.3 Association between CCI and SIS index and SIS overall recovery scale

Quantile regression models yielded significant negative associations between the CCI and the SIS index at each quartile at 3 months post-stroke after adjusting for covariates. A one-point increase on the CCI was associated with 6.80-points decrease on the SIS index at the .25 quantile (95% CI [-11.26, -2.34]; p = 0.003), with 3.58-points decrease at the median (95% CI [-5.62, -1.54]; p = 0.001) and with 1.76-points decrease at the .75 quantile (95% CI [-2.80, -0.73]; p = 0.001). At 12 months, the association followed a similar trend; however, this was only significant, based on the adjusted alpha, at the lower and upper quartiles. A one-point increase on the CCI was associated with 6.47-points decrease on the SIS index at the .25 quantile (95% CI [-11.05, -1.89]; p = 0.006) and with 1.26-points decrease at the .75 quantile (95% CI [-2.11, -0.42]; p = 0.004). Quantile regression also yielded negative associations between the CCI and the SIS overall recovery scale; however, the association was only statistically significant at the median at 3 months, and the upper quartile at 12 months. A one-point increase on the CCI was associated with 4.02-points decrease on the SIS overall recovery scale at the median (95% CI [-7.53, -0.51]; p = 0.025) at 3 months and 2.50-points decrease on the SIS overall recovery scale at the .75 quantile (95% CI: [-4.59, -0.41]; p = 0.019) at 12 months (Table 8.3).

Table 8.3

Association Between CCI and SIS Index and Overall Recovery Scale

	CCI coefficient (95% CI)	*p*	*n*
SIS index			
3 months post-stroke			
.25 quantile	-6.80 (-11.26, -2.34)	**.003**	
median	-3.58 (-5.62, -1.54)	**.001**	177
.75 quantile	-1.76 (-2.80, -0.73)	**.001**	
12 months post-stroke			
.25 quantile	-6.47 (-11.05, -1.89)	**.006**	
median	-2.57 (-5.18, 0.04)	.053	156
.75 quantile	-1.26 (-2.11, -0.42)	**.004**	
SIS overall recovery scale			
3 months post-stroke			
.25 quantile	-3.01 (-8.50, 2.49)	.281	
median	-4.02 (-7.53, -0.51)	**.025**	173
.75 quantile	-2.57 (-5.00, -0.14)	.038	
12 months post-stroke			
.25 quantile	-2.56 (-7.99, 2.88)	.354	
median	-2.27 (-4.60, 0.07)	.057	156
.75 quantile	-2.50 (-4.59, -0.41)	**.019**	

Note. The model was adjusted for age at stroke onset, sex of the stroke survivor and baseline stroke severity. Coefficients in boldface indicate statistically significant results based on the adjusted alpha ($\alpha = 0.025$).

8.5 Discussion

Our findings advance the current literature by demonstrating for the first time, to our knowledge, the independent association between comorbidity burden and patient-rated perceived stroke impact, as measured by the SIS index. The results demonstrate that greater comorbidity burden is associated with greater stroke impact, as perceived by persons with stroke, after adjustment for other factors impacting recovery – stroke severity, age and sex. The association between comorbidity burden and patient-rated perceived stroke impact was significant across all quartiles of the distribution of perceived impact at 3 months, and for the .25 and .75 quantiles at 12 months. The strength of the association was greatest in magnitude at the lower quantiles, indicating a strong association between comorbidity burden and perceived stroke impact for participants with lower scores on the SIS index (i.e., those who experienced a greater impact of their stroke) at both time points. The association between comorbidity burden and perceived overall recovery was also inverse; however, the relationship was only statistically significant at the median at 3 months, and at the .75 quantile at 12 months, post-stroke. This association may be weaker because the SIS overall recovery scale requires the respondent to make a global judgement via a single score, and may therefore be open to heuristic biases, including factors pertaining to primacy and recency.

Recovery post-stroke is complex and multi-dimensional; it may be that it cannot be adequately assessed solely by independently observed measures. In this study, our approach represents a shift in focus from utilising only observer-rated measures to using patient-rated perceived measures, to explore the impact of stroke in relation to an indicator of an individual's prior experience of health – pre-existing comorbidity burden. Existing literature has demonstrated strong associations between variants of the SIS and observer-rated outcome measures, such as the mRS and the Barthel Index; however, the purpose and design of these outcome measures differ from the SIS index. The SIS index is likely to provide a more nuanced representation of outcome because it includes items that assess for the possible presence of non-physical effects of stroke, such as memory, emotion and social participation. It may be that measures of patient-rated perceived impact are more able to account for an individual's particular circumstances and psychosocial factors. For this reason, we argue that patient-rated perceived stroke impact should be considered in the assessment of recovery, alongside conventional observer-rated measures, in order to attain a more 'complete' picture of recovery. Further, the notion of perceived impact and recovery is important in the context of the widely adopted healthcare practice of patient-centred care. Perceived impact should be central in informing clinical decision-making, individualised treatment plans and the optimal allocation of healthcare resources.

There are potential limitations to the validity and generalisability of the study. First, the participants included in this study sample significantly differed from those excluded in terms of their age, sex, stroke severity and comorbidity burden. The reason for non-inclusion was the inability to obtain data at each time point, despite all participants being contacted for follow-up according to a uniform protocol. The findings are valid relative to the characteristics of the group observed; however, they may not be valid for those excluded that had, on average, greater comorbidity burden, more severe strokes and who were older. Second, the mean age at stroke of participants included in this sample (M = 68, SD = 13) was lower than population samples (M = 73, SD = 14), as was the proportion of females (33%) compared with the Australian Stroke Clinical Registry (46%) (Cadilhac et al., 2017). Third, participants were recruited from hospitals with specialised stroke units, which may have contributed to better recovery outcomes compared with patients receiving care in hospitals without such units. Fourth, 36 included participants had undergone thrombolysis with tPA, within the first few hours of presentation, based on decisions made by their treating clinicians. While these decisions were very likely to have been influenced by patients' acute NIHSS scores on arrival at hospital, this very early phase of stroke management precedes the day 3 to 7 NIHSS score on which our current study is based. However, this does raise the question of whether the association between comorbidity burden and perceived impact and recovery, may be attenuated by acute treatments. Alternatively, it may be that patients with greater comorbidity burden are less likely to receive thrombolysis, or acute stroke rehabilitation,

which may therefore produce a pseudo-association between comorbidity burden and recovery outcomes.

We recommend that further research be undertaken to address these questions. Last, most participants in this sample (72%) experienced a stroke of mild neurological severity (Figure S3, supplement). Despite assessment modification to actively encourage their inclusion, relatively few patients with severe neurological deficits or aphasia participated in this study, limiting the findings' generalisability. The prevalence of mild stroke, however, has increased due to greater public awareness, reduction of risk factors and advances in acute stroke care. In recent times it has been suggested that half of all stroke survivors experience a mild stroke (Wolf et al., 2009); accordingly, it may be that survivors of mild stroke should be of particular interest and importance when considering recovery outcomes. Patients with mild stroke are often expected to achieve full, or close to full, recovery, and subsequently may be discharged with minimal outpatient rehabilitation and follow-up support. However, complete recovery does not occur for a substantial proportion of mild stroke survivors (Edwards et al., 2006). Our findings highlight that even for those categorised as having mild stroke, there was an independent association between pre-existing comorbidities and perceived stroke impact. Further, perceived impact of stroke has been shown to become more prominent over time; even in the case for persons with mild to moderate stroke severity (Skoglund et al., 2019).

8.6 Conclusion

Increasing comorbidity burden is associated with greater patient-rated perceived stroke impact within the first-year post-stroke – independent of age at stroke onset, sex and stroke severity. Further, our study highlights the use of patient-rated measures of perceived stroke impact; we recommend their use, alongside conventional observer-rated measures, in future stroke practice and research.

Supplementary Material

Table 8-S1.

Frequency of Premorbid Charlson Comorbidity Index (CCI) Scores (n = 177)

CCI score	Frequency	Per cent
1	53	29.94
2	2	1.13
3	92	51.98
4	8	4.52
5	18	10.17
6	2	1.13
7	0	0
8	2	1.13

Chapter 9.
General Discussion

This chapter presents an overall discussion relating to the themes and main findings that have emerged in this thesis. In addition, implications for clinical practice and recommendations for future research are presented, based on these findings. There are five sections comprising this discussion chapter, as follows:

- 9.1 Themes and Main Findings
- 9.2 Implications for Clinical Practice
- 9.3 Recommendations for Future Research
- 9.4 Limitations
- 9.5 Related Concepts Beyond the Scope of this Thesis

9.1 Themes and Main Findings

Three key themes emerged from the six main findings of this thesis. Each theme, and its related main findings, are listed below. The themes and findings are then discussed in subsequent paragraphs, in the context of current literature, and possible explanations for each finding are proposed.

Theme 1: The Prevalence and Trajectory of Post-Stroke Depression

- Finding 1: Depression is prevalent among stroke survivors.
- Finding 2: The trajectory of post-stroke depression is dynamic.

Theme 2: Screening for Post-Stroke Depression

- Finding 3: Post-stroke depression is a condition suitable for routine screening.
- Finding 4: Post-stroke depression is a condition which would benefit from screening at repeated intervals.

Theme 3: Post-Stroke Depression and the Value of Patient Perceived Recovery Outcomes

- Finding 5: Post-stroke depressive symptoms are associated with patient-reported outcomes.
- Finding 6: The use of patient-reported outcome measures provides important information relating to recovery from stroke.

9.1.1 Depression is prevalent among stroke survivors

Findings from the studies presented in this thesis add further evidence for the high prevalence of depression following stroke. The prevalence of depressive symptoms in the START cohort (N = 219) was consistently high at each time point: 42, 46 and 38 per cent, respectively, as described in Chapter 4. The prevalence of depressive symptoms in the sample of participants, from the START cohort, who recorded MADRS scores at all time points (n = 142), analysed in Empirical Research Study 1 (Chapter 5) was also consistently high: 39, 43 and 35 per cent, respectively. This is comparable to the pooled prevalence of 31 per cent (95% CI [28, 35]) within the first five years reported by Hackett and Pickles (2014), and 29 per cent (95% CI [25, 32]) during the first 10 years reported by Ayerbe et al. (2013a), in their respective meta-analyses. Further, in the sample (n = 142) analysed in Empirical Research Study 1 (Chapter 5), 90 (63%) stroke survivors experienced depressive symptoms at one or more time points over the course of the first year after stroke. This is comparable to the cumulative incidence of up to 52 per cent within five years post-stroke reported by Ayerbe et al. (2013) in their meta-analysis.

The prevalence of depressive symptoms observed in the START cohort (Chapter 4) and in the sample presented in Empirical Research Study 1 (Chapter 5) is higher than the prevalence reported by the two meta-analyses (Hackett & Pickles, 2014; Ayerbe et al., 2013a). This may be due to several reasons, including:

- the use of a screening measure in lieu of a diagnostic assessment;
- the cut-off score selected to determine the presence of depressive symptoms; and
- the study duration.

A screening measure for depressive symptoms (MADRS) was used in the START cohort (Chapter 4) and in the sample analysed in Empirical Research Study 1 (Chapter 5). In contrast, the meta-analyses included studies that employed diagnostic interviews in addition to studies that utilised various screening measures. This difference may have contributed to the higher prevalence of depressive symptoms observed in the START cohort and sample. Studies that use a screening tool tend to overestimate the prevalence of depression, compared to studies that utilise a diagnostic assessment of depression (Ayerbe et al., 2013a; Gaete & Bogousslavsky, 2008). The purpose of a screening measure for depressive symptoms is to identify the likely, or possible, presence of depression. If depressive symptoms are detected on a screening measure, this should initiate a diagnostic assessment which subsequently confirms, or refutes, a diagnosis of depression.

In addition, the selection of the cut-off score in a screening measure also influences the observed prevalence of depressive symptoms. Accordingly, another possible explanation for the higher prevalence in the START cohort and sample was the use of a cut-off score set at ≥ 7 on the

MADRS. This threshold has been utilised in several previous stroke cohort studies (Snaith et al., 1986; Verdelho et al., 2004). The selection of a higher cut-off score, for example ≥ 8 (Sagen et al., 2009), would have reduced the observed prevalence of depressive symptoms.

Last, the duration of the study period, and the time point at which prevalence is estimated, also affects the observed prevalence of depression. This is because the timing of onset, the course and the duration of post-stroke depression varies (Ayerbe et al., 2013b). The study duration of the START research program was 12 months and the prevalence of depressive symptoms was calculated at three time points within this study period (Carey et al., 2015). In contrast, the meta-analyses included studies which utilised different durations, up to one decade following stroke. Further, each meta-analysis included studies with assessment time points ranging widely, from "2 to 5 days" to "5 years" after stroke (Hackett & Pickles, 2014) and from "within 1 month" to "10 years" post-stroke (Ayerbe et al., 2013a).

9.1.2 The trajectory of post-stroke depression is dynamic

Evidence for the dynamic trajectory of depressive symptoms within the first year was demonstrated in Empirical Research Study 1 (Chapter 5). In this study, of the 142 stroke survivors, 68 (48%) experienced a change in depressive symptom status from 'present' to 'absent' or vice-versa, over the course of the first year post-stroke. These findings add to those of existing longitudinal studies that explore post-stroke depression.

The review (Chapter 2) presented 63 longitudinal, prospective, observational, cohort studies exploring the trajectory of post-stroke depression. The earliest study to extend to three years following stroke (into the 'chronic extended' phase) was that conducted by Åström et al. (1993). These authors showed that the prevalence of post-stroke depression appears to change over time. In this sample of stroke survivors, the prevalence peaked at 3 months, declined at 12 months, increased again at 2 years, and continued to increase at 3 years. Two decades later, Ayerbe et al. (2013b) demonstrated the dynamic nature of post-stroke depression in a large, prospective, longitudinal study over 15 years. These authors stated that post-stroke depression varies significantly in timing of onset, course and duration. Their study demonstrated that many stroke survivors experience recurring episodes of post-stroke depression, up until 15 years post-stroke (Ayerbe et al., 2013b).

Several factors may contribute to the variation of depressive symptom status over time. In the acute phase, psychological symptoms secondary to the sudden, complex and potentially catastrophic nature of stroke, such as grief, uncertainty and fear, may be exhibited. In addition, somatic symptoms, such as fatigue, psychomotor retardation, reduced concentration, sleep disturbance and reduced appetite, can occur due to cerebrovascular damage following stroke (de

Coster et al., 2005; Cumming et al., 2010). Such psychological and somatic symptoms are also criteria for the diagnosis of depression. This overlap can further complicate the assessment of 'true' depression and may contribute to an artificial inflation of the prevalence of depression, particularly in the acute phase post-stroke. Conversely, in acute and subacute phases, stroke survivors may not have become fully cognisant of the extent of their limitations, and depressive symptoms may not initially be apparent (Gaete & Bogousslavsky, 2008). This potentially contributes to an underestimation of depressive symptoms in the early phases following stroke.

The process of a stroke survivor developing an understanding of the full impact of their stroke is likely to extend over time. In the subacute phase, many stroke survivors will have been discharged or transferred from acute care to rehabilitation services, to supported residential care or to their homes. It may be that depressive symptoms become apparent at, or after, these transitions, when stroke survivors attempt to resume participation in their usual daily activities and roles (Tellier & Rochette, 2009). Many stroke survivors experience significant adjustments to their living arrangements, changes in roles and relationships and an increased reliance on others. By this time, they may be more likely to have become aware of any residual stroke-related deficits and long-term impacts (White et al., 2012). Further, stroke survivors may be more likely to experience depressive symptoms if they are socially isolated or lack family and community support. These contextual factors are likely to contribute to the apparent latency of onset of depression in many stroke survivors.

9.1.3 Post-stroke depression is a condition suitable for routine screening

Post-stroke depression is a condition that is eminently suitable for routine screening, as highlighted in the Perspective Article (Chapter 6). Evidence for this is based on criteria, originally developed by Wilson and Jungner (1968), and adapted by the World Health Organisation (World Health Organisation, 2020). These criteria are widely used to determine suitability for routine screening. They are listed below, and are discussed in subsequent paragraphs:

i. The condition is an important health problem.
ii. It has a reasonably high prevalence.
iii. It has a detectable latent phase.
iv. There are validated screening measures with defined cut-off scores.
v. The screening measures are relatively brief and easy to administer.
vi. The use of screening measures is acceptable to the target population.
vii. There are effective treatments for the condition.
viii. The benefits of screening outweigh any potential harm.

i. The condition is an important health problem.

Post-stroke depression is an important health problem because it is known to adversely affect stroke patients' ability to participate in rehabilitation and is associated with worse recovery outcomes (Ayerbe et al., 2013a; Robinson & Jorge, 2016). Examples of such outcomes include: increased risk of mortality (Ayerbe et al., 2013a; Kutlubaev & Pickles, 2014; Cai et al., 2019); increased disability (Ayerbe et al., 2013a; Kutlubaev & Pickles, 2014); greater dependence in activities of daily living (Chemerinski et al., 2001; Amaricai & Poenaru, 2016; Paolucci et al., 2019); reduced participation in work and social activities (Tse et al., 2017a; Tse et al., 2019); and poorer quality of life (Kwok et al., 2006).

ii. It has a reasonably high prevalence.

It is frequently reported that one in three stroke survivors experience depression (Ayerbe et al., 2013a; Hackett & Pickles, 2014). This figure is supported by the high prevalence of depressive symptoms observed in Empirical Research Study 1 (Chapter 5); of 142 stroke survivors, 63 per cent experienced depressive symptoms at one or more assessment time points, during the first year post-stroke.

iii. It has a detectable latent phase.

To meet the threshold of depressive symptoms 'present' on a screening measure, symptoms are assessed over a preceding time period, usually of one week (for example, MADRS SIGMA and CES-D) or two weeks (for example, BDI and PHQ-9). Similarly, to fulfil the criteria of depression on a diagnostic assessment, such as the DSM, symptoms must be persistent and experienced over at least the preceding two weeks (American Psychiatric Association [APA], 2013a). These requirements recognise that the onset and development of depression is gradual, rather than abrupt. This latency of onset provides an opportunity to identify depression, early in its course or prior to its full expression.

iv. There are validated screening measures with defined cut-off scores.

There are numerous validated screening tools available to identify post-stroke depression (Meader et al., 2014; Prisnie et al., 2016). In the START research program, the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) was selected for use. In the review (Chapter 2), 11 other validated assessments of depression or depressive symptoms were identified across the 63 included studies. These measures included: Hospital Anxiety and Depression Scale – Depression subscale (HADS-D) (Zigmond & Snaith, 1983), Centre for Epidemiological Studies – Depression (CES-D) (Radloff, 1977), Beck Depression Inventory (BDI) (Beck, 1961), Geriatric Depression Scale (GSD) (Yesavage, 1983), Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and Patient Health Questionnaire (PHQ) (Spitzer et al., 1994; Kroenke et al., 2001). There was variation in the selection of cut-off score used for each

measure, across different studies. In the Perspective Article (Chapter 6), it was suggested that screening for depression be undertaken using a validated measure. Although each measure has its advantages, there is no strong evidence to suggest that one measure is more suitable than the others, for stroke cohorts (Meader et al., 2014; Prisnie et al., 2016; Das & Rajanikant, 2018). In practice, brief outcome measures are favourable because they minimise patient and clinician burden. However, there is a trade-off between brevity of a measure and comprehensiveness that ensures precision.

v. The screening measures are relatively brief and easy to administer.

The screening measures identified in the review (Chapter 2) vary in their number of items, and the time required to administer – but all are generally brief, ranging from approximately 5 to 20 minutes. A range of health professionals, including nurses, occupational therapists, psychologists, general practitioners and medical specialists, can administer the screening measures (Nease & Malouin 2003; Rogers, 2017). In addition, the assessments can be undertaken in a variety of settings, such as in acute hospitals, in rehabilitation centres, in residential care, at patients' homes or in General Practice (GP) clinics. Further, some screening instruments have online versions and smart phone applications, which can facilitate their accesibility and use.

vi. The use of screening measures is acceptable to the target population.

Screening measures for depression have been validated in stroke cohorts and are acceptable for use in practice (Meader et al., 2014). In general, they are relatively simple questionnaires and mostly utilise a Likert scale for responses. Screening measures necessitate the respondent to actively participate with informed consent. The questionnaires are usually administered by clinicians or researchers trained in the conduct of their use (Rogers, 2017). Further, these clinicians and researchers should be empathetic and supportive in the administration of screening measures, given the often sensitive and sometimes difficult nature of discussing mental health concerns. Importantly, stroke survivors can decline or withdraw participation from the interview or assessment, at any time.

vii. There are effective treatments for the condition.

Although evidence for effectiveness of treatments for post-stroke depression remains somewhat inconclusive, numerous studies have demonstrated positive effects of psychological interventions (including the provision of counselling and psychosocial support) (Wang et al., 2018; Majumdar & Morris, 2018; Cheung, 2019) and pharmacological treatments (such as the prescription of antidepressant medication) (Robinson & Jorge, 2016; Starkstein & Hayhow, 2019; Mortensen & Andersen, 2021).

viii. The benefits of screening outweigh any potential harm.

The benefit of screening for depressive symptoms after stroke is that it leads to the diagnosis of depression, if present. The diagnosis should initiate appropriate treatment and management, contributing to better outcomes, recovery, and quality of life. Overall, the benefit of screening outweighs the potential harm of undertaking a screening measure – as long as it is undertaken in an ethical and sensitive manner. The patient should be provided with sufficient information about the screening measure and process, including its purpose, the possible outcomes and options available to them in response to an outcome (Goyder et al., 2000).

The purpose of screening stroke survivors for depression is to identify those who are likely to meet the criteria for a diagnosis of depression. The value of a diagnosis is, primarily, that it should initiate the provision of treatment and management. However, in clinical practice, the ability to screen, diagnose and provide timely and appropriate treatment depends on several factors, including the availability of resources. A diagnosis of depression itself can be of value to a stroke survivor because the intrinsic nature of a diagnosis can help an individual to understand their symptoms, to reduce uncertainty, to validate their experience, and to instil hope for recovery. However, receiving a diagnosis, in some cases, may have unintended negative consequences, especially if treatment is limited or not available. Nevertheless, if a diagnosis is provided with sensitivity, with clear information, with time for discussion, and with a sense of hope – it is likely to be experienced more positively by the individual (Perkins et al., 2018).

9.1.4 Post-stroke depression is a condition which would benefit from screening at repeated intervals

Currently, screening for depression, when undertaken, appears to be concentrated within the first few months after stroke (White et al., 2012). Screening only in the acute phase, however, may result in patients being categorised as 'not depressed', and subsequently not being reviewed at later stages (Shankar et al., 2017). Post-stroke depression is dynamic, with new cases of depression, and recovery from depression, occurring over time (Ayerbe et al., 2013b; Das & Rajanikant, 2018). Further evidence for the dynamic trajectory of post-stroke depression is demonstrated in Empirical Research Study 1 (Chapter 5). Of the 87 stroke survivors assessed as not having depressive symptoms within the first week, one-third (29/87, 33%) experienced depressive symptoms at 3 months. Of these 29 stroke survivors, two-thirds (19/29, 66%) continued to experience depressive symptoms at 12 months.

Our finding is comparable to the finding reported by Ayerbe et al. (2013b) that although most episodes of depression begin within the first year, one-third of these do not start until after 3 months post-stroke – and may not emerge until many months later. Further, in Empirical Research Study 1 (Chapter 5) at 12 months, 6 of the 50 (12%) stroke survivors with depressive symptoms

had not experienced these symptoms prior to the 12 month assessment. Similarly, Ayerbe et al. (2013b) found 85 of 518 (16%) stroke survivors had depressive symptoms detected for the first time at 12 months. Accordingly, post-stroke depression is a condition which would benefit from screening at repeated intervals.

9.1.5 Post-stroke depressive symptoms are associated with patient-reported outcomes

Empirical Research Study 2 (Chapter 7) demonstrated independent associations between depressive symptoms and recovery outcomes at 3 and 12 months following stroke. These associations were significant only for patient-reported outcome measures – but not for the observer-rated outcome measure. A possible explanation for this observed discrepancy may be related to the source of responses for the measure – the patient or the clinician. Patient-reported outcome measures appear to enable stroke survivors with depressive symptoms to express, in some way, the impact of these symptoms. When a patient-reported outcome measure includes a 'mood' or an 'emotion' domain, the impact is likely to be expressed directly. However, when a patient-reported outcome measure does not incorporate a mood or emotion domain, the impact of depressive symptoms may be still expressed. This could occur indirectly via a related construct (for example, the construct of 'participation' on the WSAS), or by less positive responses to items in other domains (for example, items relating to physical function on SIS-16).

9.1.6 The use of patient-reported outcome measures provides important information relating to recovery from stroke

The use of patient-reported outcome measures, alongside observer-rated outcome measures, provides important information for stroke clinicians and researchers. In Empirical Research Study 2 (Chapter 7), significant associations were demonstrated between depressive symptoms and patient-reported recovery outcomes at 3 and 12 months post-stroke. Further, in Empirical Research Study 3 (Chapter 8), significant associations were found between comorbidity burden and patient-reported recovery outcomes within the first year following stroke. Collectively, these findings highlight the value of patient-reported recovery outcomes by demonstrating that they appear to capture the impact of depressive symptoms and comorbidity burden on recovery post-stroke. The outcomes that concern a clinician are not always the outcomes that matter most to stroke survivors (Hannah et al., 2014). Patient-reported outcome measures provide useful insights into a stroke survivor's perception of their own recovery – by providing meaningful information about their expectations, needs and values (Ytterberg et al., 2017). Further, patient-reported outcome measure are sensitive to change (Stewart & Cramer, 2013). Evidence indicates that stroke survivors who are active participants in their own rehabilitation are more likely to experience better recovery (Ytterberg et al., 2017; Katzan et al., 2017). The routine use of patient-reported outcome measures facilitates collaborative decision making and aligns with the widely adopted healthcare practice of patient-centred care (Reeves et al., 2018).

9.2 Implications for Clinical Practice

The findings in this thesis have important implications for clinical practice. There are six primary implications, which are discussed in this section under the following subheadings:

- Increase clinician awareness of post-stroke depression
- Update clinical guidelines
- Establish and promote referral pathways
- Include screening results on discharge reports
- Increase stroke survivor and family awareness of post-stroke depression
- Utilise patient-reported outcome measures in clinical practice

9.2.1 Increase clinician awareness of post-stroke depression

In this thesis, Empirical Research Study 1 (Chapter 5) confirmed that post-stroke depression is common and has a dynamic trajectory. Despite this, the Perspective Article (Chapter 6) highlighted that in current Australian practice there may be large numbers of stroke patients with undetected depression, because only half undergo mood assessment (National Stroke Foundation, 2020). Further, current national guidelines fail to recommend routine and repeated screening – despite evidence to the contrary, as described in the Perspective Article (Chapter 6). Therefore, all clinicians working in acute stroke care and in rehabilitation centres should be aware of post-stroke depression and its characteristics – including its prevalence, trajectory and impact. Increased clinician awareness of post-stroke depression can be achieved by the provision of education and resources. In addition, specific training in the use of validated screening assessments can increase clinician confidence in assessing and discussing mental health concerns with their patients. These recommendations align with those advised by Hackett and Pickles (2014) who suggested all stroke-related clinicians would benefit from training in the use of validated measures for depression.

Empirical Research Study 1 (Chapter 5) also confirmed the commonly observed latency of onset of post-stroke depression, with many stroke survivors experiencing depressive symptoms, for the first time, at the 3 or 12 month time points. By these stages, many stroke survivors will have been discharged home, where they are managed by community health services, including their general practitioner (GP). Therefore, the provision of education and resources regarding post-stroke depression should be extended to include community health clinicians and GPs. Stroke survivors continue to experience depressive symptoms in the chronic phase after stroke (Andrew et al., 2014; Crichton et al., 2016). A national survey found 84 per cent of stroke survivors, at least 12 months post-stroke, reported ongoing psychological concerns including depressive symptoms

(Andrew et al., 2014). Therefore, it is important that GPs and community health clinicians continue to routinely screen for depression in chronic phases following stroke.

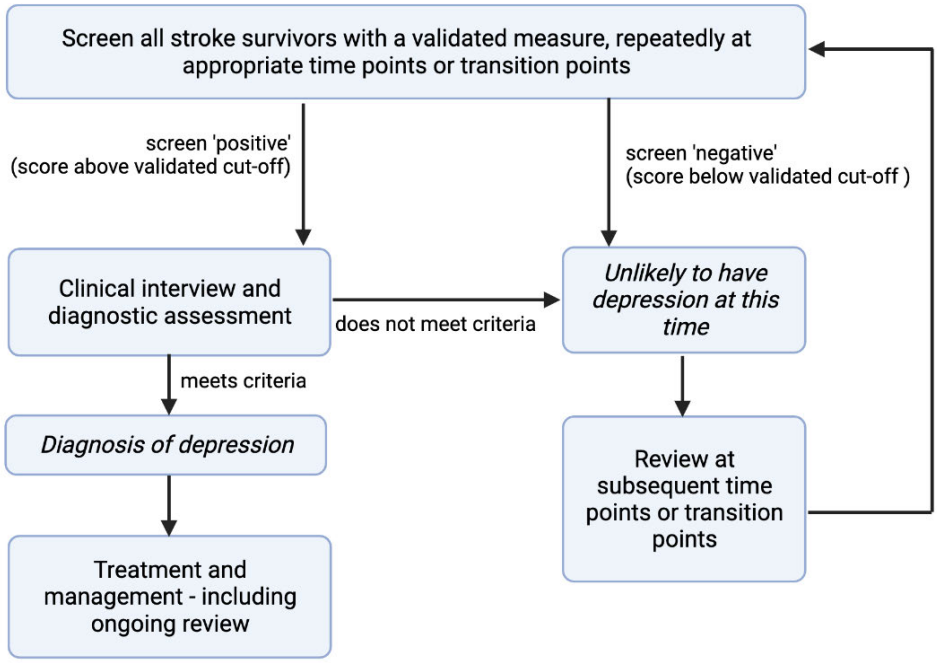
9.2.2 Update clinical guidelines

It is important that all stroke survivors are screened for depression repeatedly, at appropriate intervals, because post-stroke depression is prevalent and has a dynamic trajectory, as confirmed by Empirical Study 1 (Chapter 5). This study also indicated that screening only in the acute phase may risk missing stroke survivors with later onset of depression. Empirical Research Study 1 (Chapter 5) and the Perspective Article (Chapter 6) recommended that screening for post-stroke depression be undertaken not only in the acute phase, but also during the subacute and chronic phases. Screening for post-stroke depression could be undertaken at specific time points (for example, at 1 month, 3 months, 6 months, 12 months and periodically thereafter), or at transition points along the continuum of care (for example, at transfer from acute to rehabilitation services, and at discharge to home). Alternatively, screening could be effectively undertaken using a schedule that combines both time points and transition points. The Perspective Article (Chapter 6) highlighted that such a schedule has been advised by the National Clinical Guideline for Stroke in the United Kingdom, recommending screening within the first 6 weeks, at transfer into post-acute services and at follow-up at 6 and 12 months post-stroke (Royal College of Physicians, 2016). The establishment of an effective plan to address regular screening for depression in stroke cohorts could lead to a reduction in post-stroke depression (Cai et al., 2019). As stated in the Perspective Article (Chapter 6), it is recommended that current Australian Clinical Guidelines for Stroke Management (National Stroke Foundation, 2021) be updated to promote routine and repeated screening for post-stroke depression. These guidelines are widely promulgated among health professionals and services managing stroke patients, and therefore are likely to be effective in influencing clinical practice.

A proposed flow chart for the screening and subsequent diagnosis of post-stroke depression is presented in Figure 9.1. This has been adapted from an algorithm developed for diagnosing depression in general medical conditions (Gold et al., 2020). This proposed version has been modified specifically to reflect the need for routine and repeated screening in post-stroke depression.

Figure 9.1

Proposed Flow Chart for the Screening and Diagnosis of Post-Stroke Depression



In this proposed flow chart, if a stroke patient screens 'negative' on a screening measure, or if they screen 'positive' but do not meet the criteria for depression following diagnostic interview, they are unlikely to have depression at that time. However, all such patients should be included in ongoing screening, at appropriate intervals.

Based on the findings from Empirical Research Study 1 (Chapter 5), the Perspective Article (Chapter 6) and international guidelines, the routine screening for depression in all stroke survivors is recommended, using a schedule that combines both specific time points (for example, at 3 months post-stroke) and transition points along the continuum of care (for example, at transfer from acute to rehabilitation services, or at discharge to home). Further, clinicians should consider undertaking ongoing screening at regular intervals beyond the acute phase, for example, every 3 to 6 months during the first 12 months, and every 6 to 12 months during subsequent years. The optimal frequency of screening for depression is still to be determined – and will likely be impacted by feasibility and availability of resources.

9.2.3 Establish and promote referral pathways

The implication of updating clinical guidelines to promote routine and repeated screening for post-stroke depression is that sufficient resources will need be available to manage stroke survivors who screen 'positive' for depressive symptoms. Clear referral pathways for diagnostic

assessment of depression should be established, and local referral pathways should be promoted to clinicians. Following the formal psychiatric interview, stroke survivors with confirmed depression should receive appropriate treatment, management and follow-up. Hackles and Pickles (2014) advocated for increased clinician awareness of institutional referral pathways and guidelines for screening for and the management of post-stroke depression.

9.2.4 Include screening results on discharge reports

Discharge summaries from acute and rehabilitation services should include information about post-stroke depression. For example, reports should include the screening instrument and cut-off point used, the stroke patient's score, the date of administration, and any other relevant clinical information. Further, discharge reports should recommend repeated screening for post-stroke depression, with reference to subsequent time points or transition points, which reflect updated national guidelines. The inclusion of information pertaining to post-stroke depression, including the patient's score on a screening measure, will help to strengthen communication between clinicians in different settings, at different stages, along the continuum of care.

9.2.5 Increase stroke survivor and family awareness of post-stroke depression

In the sample of stroke survivors analysed in Empirical Research Study 1 (Chapter 5), almost half (43 per cent) screened 'positive' for depressive symptoms at the 3 month time point. At this time, many of these predominantly mild stroke survivors were likely to have been discharged home – often into the care of their families. The provision of education regarding post-stroke depression to stroke survivors and their family caregivers, prior to this transition to home, aligns with the practice of patient-centred care (Cramm & Nieboer, 2018). By providing education about post-stroke depression to family caregivers, they are more likely to be able to recognise depressive symptoms in the stroke survivor and report this to clinicians, mitigating the risk of delayed detection (Klinedinst et al., 2012; Zulim et al., 2019).

9.2.6 Utilise patient-reported outcome measures in clinical practice

Empirical Research Study 2 (Chapter 7) demonstrated the association between depressive symptoms and patient-reported outcome measures. Further, Empirical Research Study 3 (Chapter 8) showed that comorbidity burden is also associated with patient-reported outcome measures. These findings highlight the value of using patient-reported outcome measures in the assessment of overall recovery post-stroke. Patient-reported outcomes are underutilised in stroke clinical practice (Reeves et al., 2018; Schindel et al., 2019). Accordingly, clinicians should utilise patient-reported outcomes measures, alongside observer-rated outcome measures. Based on the findings in Empirical Research Studies 2 and 3 (Chapters 7 and 8), the use of the SIS and the WSAS, or other patient-reported outcome measures, in the evaluation of overall recovery after stroke is recommended. The routine use of patient-reported outcome measures facilitates collaborative

decision making, and stroke survivors who are active participants in their own rehabilitation are more likely to experience better recovery (Ytterberg et al., 2017; Katzan et al., 2017). The value of using patient-reported outcome measures in clinical practice has been discussed in the Themes and Main Findings section (9.1.6 The use of the patient-reported outcome measures provides important information relating to recovery from stroke).

9.3 Recommendations for Future Research

Based on the main findings of this thesis, several recommendations for future research have emerged. Each recommendation is explained under the following subheadings:

- Conduct longitudinal cohort studies with multiple assessment time points.
- Define time points using quantifiable units of time to facilitate comparison.
- Establish the optimal timing of screening for post-stroke depression.
- Utilise patient-reported outcome measures in research.
- Explore the course of specific post-stroke depressive symptoms.

9.3.1 Conduct longitudinal cohort studies with multiple assessment time points

We recommend researchers undertake longitudinal cohort studies to improve current understanding of the trajectory of post-stroke depression and to assist in determining optimal schedules for screening. Based on our findings from the review (Chapter 2), it is recommended that such longitudinal studies include a minimum of two time point assessments, but preferably more, with a study duration that extends to at least 12 months post-stroke.

9.3.2 Define time points using quantifiable units of time to facilitate comparison

Longitudinal cohort studies should define and report each assessment time point using a quantifiable unit of time post-stroke (such as days, weeks or months). The advantage of this is that it facilitates the precise comparison of results across different studies. For example, scores on an assessment undertaken at a particular time point which is defined as ‘a mean of 17 days following stroke onset, with a standard deviation of 3.2 days, and a range of 12 to 21 days’ can be accurately used in comparison with other studies – across different settings, different countries and different eras. In contrast, it is difficult to make precise and meaningful comparisons when studies describe the timing of their assessments as time periods, for example ‘within the first eight weeks of admission’ (without reporting the corresponding measures of central tendency and dispersion). Similarly, studies that present findings in relation to undefined time points, for example described only as ‘time point 1’, ‘time point 2’ and so on, are also problematic for comparison. Further, studies that describe assessment time points using a clinical event post-stroke, for example ‘at discharge from acute care’ or ‘at discharge home’ also present problems. This description may be useful because the trajectory of depression after stroke may be influenced by such events and may

be an appropriate opportunity to screen for depression. However, for the purposes of consistent research methodology and comparison, it is recommended that such events should also be described by a quantifiable measure of time post-stroke, such as 'at transfer from acute to rehabilitation services, between 7 to 21 days post-stroke.'

9.3.3 Establish the optimal timing of screening for post-stroke depression

Further longitudinal research to establish an optimal schedule of screening for post-stroke depression is recommended. Such studies should include multiple assessment time points over a minimum duration of one year. In Empirical Research Study 1 (Chapter 5), the 3 month time point appears to be important in the context of post-stroke depression. At this time point, there was a high prevalence of depressive symptoms, and most participants who had depressive symptoms at 12 months had experienced such symptoms at 3 months. Although the START research program did not utilise transitions as assessment time points, it may be of value in future research to include assessment points based around transitions – but which are also defined by the number of days, weeks or months post-stroke. Thayabaranathan and colleagues highlighted the likely benefit of screening for post-stroke depression at transition points, particularly at the transition home (Thayabaranathan et al., 2018).

9.3.4 Utilise patient-reported outcome measures in research

In order to attain a more complete understanding of the impact of post-stroke depression on recovery, we recommend the routine use of patient-reported outcome measures in research, together with observer-rated outcome measures. Collectively, the findings from Empirical Research Study 2 and 3 (Chapter 7 and 8) highlight the value of patient-reported outcome measures by showing that they appear to capture the impact of depressive symptoms and comorbidity burden on post-stroke recovery. The importance of using patient-reported outcome measures has been discussed in the Themes and Main Findings section (9.1.6 The use of the patient-reported outcome measures provides important information relating to recovery from stroke).

Further, we recommend the development and validation of a new stroke-specific outcome measure that incorporates input from both patient and clinician. A 'dual source' measure such as this could include the following design features and characteristics:

- The measure should collect responses from both the patient and the clinician or observer, separately but contemporaneously.
- The measure should evaluate 'overall recovery' by incorporating constructs which reflect the entire range of post-stroke deficits and limitations including impairments which may be subtle, such as depressive symptoms.
- The patient-reported and observer-rated parts of the measure should have corresponding constructs or domains, each comprised of equivalent items.

- The patient-reported and observer-rated parts should be designed to each yield individual domain scores and an overall index score.
- Patient-reported and observer-rated scores should be able to be directly compared.

The advantage of a dual source outcome measure such as this is that it should be able to identify the needs and concerns of the patient – alongside the clinician's assessment of that patient. If discrepancies between patient-reported scores and observer-rated scores are identified, in one or more domains, these may highlight unmet needs experienced by the stroke survivor and should be discussed with the patient and their family. In this way, such a measure would promote collaborative, patient-centred care.

9.3.5 Explore the course of specific post-stroke depressive symptoms

To advance our understanding of the phenotypes of post-stroke depression at different times following stroke, we recommend research that examines specific depressive symptoms, or clusters of symptoms, over time. This could be achieved by analysing scores of individual items from screening measures for depressive symptoms, at different time points. For example, to explore the presence and severity, over time, of the symptom 'lassitude' following stroke, items relating specifically to this symptom could be identified (for example, item 7 on the MADRS). Similarly, to explore the presence and severity, over time, of 'suicidal ideation', items corresponding to this symptom could be identified (for example, item 10 on the MADRS). Progressive scores on individual items, at different time points across different post-stroke phases, could be examined and compared. This research could facilitate the distinction between symptoms of 'true' post-stroke depression, as characterised by the DSM, and symptoms of other conditions that may occur concurrently, which may appear to be similar. Examples include:

- endogenous depression not associated with, nor caused by, stroke
- psychological symptoms that are a consequence of an acute adverse health event (such as grief, uncertainty, denial and hopelessness)
- somatic symptoms due to cerebrovascular damage following stroke (such as lassitude, reduced concentration, insomnia and reduced appetite) (de Coster et al., 2005)

9.4 Limitations

This section discusses possible limitations and caveats recognised in the empirical research studies (Chapters 5, 7 and 8) presented in this thesis. Each are discussed under the following subheadings: attrition and missing data, possible confounding factors, and the dichotomisation of continuous variables.

9.4.1 Attrition and missing data

Attrition refers to the loss of participants over the course of the study and is a common methodological problem in longitudinal research (Twisk & de Vente, 2002). In the empirical research studies presented in this thesis, reasons for attrition from baseline to 12 months were categorised as 'death', 'withdrawal' or 'loss of contact'. Despite attempts by START program researchers to actively encourage the ongoing participation of all stroke survivors, some attrition did occur. By day 3 to 7, there had been 3 deaths; by 3 months, there had been 12 further deaths, 2 withdrawals and 2 losses of contact. To replace these 19 lost participants, a further 19 were recruited in order to meet the planned sample size of 200 at the 3 month time point (Carey et al., 2015). By 12 months, there were 179 remaining participants (9 further deaths, 3 further withdrawals and 9 further losses of contact).

In addition to attrition, the problem of missing data was encountered, despite efforts by START program researchers to minimise this. The START program comprised a comprehensive suite of assessments at each time point, including questionnaires, brain imaging and pathology blood tests. This may have imposed a substantial burden of time and effort on the part of participants which may have inadvertently contributed to some individuals not completing every assessment. In Empirical Research Study 1 (Chapter 5), participants were required to have a MADRS score recorded at every time point to be included in the analysis. Of the 179 participants who completed the 12 month study, 142 had MADRS scores recorded at every time point (37 instances of missing data). In Empirical Research Study 2 (Chapter 7), participants who recorded a MADRS score, the relevant outcome measure score and all covariates (age, sex and NIHSS score) were included for analysis. At 3 months, after attrition and replacement, the total cohort comprised 200 participants; sample sizes for each analysis ranged from $n = 168$ (32 instances of missing data) to $n = 175$ (25 missing). At 12 months, after attrition, the total sample comprised 179 participants; sample sizes ranged from $n = 154$ (25 missing) to $n = 162$ (17 missing). In Empirical Research Study 3 (Chapter 8), participants who recorded a CCI score and all covariates (age, sex and NIHSS score) were included for analysis. At 3 months, sample sizes for each analysis were $n = 173$ (37 instances of missing data) and $n = 177$ (33 missing). At 12 months, sample sizes for each analysis were $n = 156$ (17 missing) and $n = 156$ (21 missing).

Because of reduced sample sizes caused by attrition and missing data, the clinical and demographic characteristics of participants included were compared with those non-included, in each of the empirical research studies (Chapters 5, 7 and 8). Participants included in all analyses, in each empirical research study, were significantly younger and had milder neurological deficits (NIHSS, day 3 to 7) compared to those non-included. In addition, in Empirical Research Study 3 (Chapter 8), there was a significantly greater number of males included, compared to those non-

included. Attrition and missing data are inevitable in large longitudinal cohort studies, and both can contribute to biased inferences from findings and impact on generalisability.

9.4.2 Generalisability

Generalisability is used to determine if a study's findings are representative of the population or an artefact of design or methodology of the study (Kukull & Ganguli, 2012). The generalisability of the findings can be impacted, if participants who were included in a particular analysis differed from those non-included, because they either dropped out of the study or did not complete a measure at a certain time point – required for a certain analysis. To explore the generalisability of the findings from the empirical research studies presented in this thesis, key characteristics of the START cohort were compared to those of the Australian Stroke Clinical Registry (AuSCR) cohort (Breen et al., 2020) (Table 4.6). There were differences between the two databases. The START cohort comprised only participants with ischaemic stroke, whereas AuSCR collected information regarding patients with all types of stroke. All START participants were managed in specialised stroke units; in contrast, 85 per cent of AuSCR registrants were managed in such units. Overall, in comparison to the AuSCR data, the START cohort was younger, had milder strokes and comprised more male participants. One possible reason for the smaller number of stroke survivors with severe neurological deficits (including communication, cognitive and mobility impairments) in the START cohort, is that such individuals may have been less likely to be able to participate in a longitudinal study. These participants, or their legally responsible family member, may have been more likely to decline an invitation to participate in the study. Further, stroke survivors with severe neurological deficit may have been more likely to withdraw or die. Last, for the START cohort, all 19 hospital recruitment sites had specialised stroke units, which may have contributed to better outcomes during acute care.

9.4.3 Possible confounding factors

Other factors may influence the presence, severity, course and duration of post-stroke depression. The START research program collected data relating to many of these factors. For example, a previous history of depression was captured by estimating a pre-stroke PHQ-2 score (≥ 3), and by recording the use of prescription antidepressant medication prior to stroke onset – as a surrogate marker for pre-stroke depression. Based on PHQ-2 scores, 50 of the 219 participants (22.83%) had a history of pre-stroke depression; based on antidepressant use prior to the stroke, 22 participants (10.05%) had a history of pre-stroke depression. Ten participants (4.57%) had pre-stroke depression based on PHQ-2 scores and were also taking antidepressant medication. Antidepressant medication is sometimes prescribed for conditions other than depression, such as chronic pain, bladder instability, insomnia or anxiety. This data, relating to pre-stroke depression, was not included in the analyses in the empirical research studies. Previous research using START program data had not observed a relationship between history of pre-stroke depression

and depressive symptoms assessed at the 3 month time point post-stroke, using either measure (Tse et al., 2017a).

Empirical Research Study 1 (Chapter 5) did not account for the following factors, which may influence the trajectory of post-stroke depression:

- Demographic characteristics including age at stroke onset and sex of the stroke survivor
- Psychological factors including pre-stroke depression, post-stroke anxiety and treatment for post-stroke depression
- Stroke-related factors such as stroke severity, lesion location, communication deficits and cognitive impairment
- Psychosocial and contextual factors such as family and social supports, relationship or marital status, employment status and financial resources

Empirical Research Studies 2 and 3 (Chapters 7 and 8) controlled for age, sex and stroke severity – but not for the other aforementioned factors. It is already known that age, sex and stroke severity independently influence recovery post-stroke (Knoflach et al., 2012; Bushnell et al., 2014; Rost et al., 2016). For the other factors, the evidence for influence on post-stroke depression and recovery remains somewhat unclear (Aron et al., 2015; Robinson & Jorge, 2016; Sangam, 2018).

9.4.4 Dichotomisation of continuous variables

The MADRS yields scores that produce a continuous variable. However, in Empirical Research Study 1 (Chapter 5), scores were dichotomised because a binary outcome is a characteristic of a screening tool used in clinical practice to determine the possible or likely presence of depression. Further, in this study, dichotomisation of MADRS scores was necessary in order to perform the required logistic regressions and to create the trajectory diagram. The dichotomisation of continuous variables to define outcomes, such as depressive symptoms 'present' or 'absent', is known to have disadvantages. First, scores which are close, but on opposite sides of the cut-off, are characterised as different when they may represent participants whose characteristics are similar. Second, the dichotomisation of continuous variables may limit the ability to detect a significant change in scores or shift in outcome (Duncan et al., 2000). Individuals with scores close to the threshold, which change at the subsequent assessment, by even only one point, may appear to have experienced a substantial change in status. Despite these disadvantages, the dichotomisation of a continuous variable is appropriate for the purpose and use of a screening measure. The function of a screening tool with a validated cut-off score is to produce a binary outcome to inform the decision to conduct further assessment – in this case, further psychiatric assessment for the diagnosis of depression. In contrast, in Empirical Research Study 2 (Chapter

7), MADRS scores were preserved as a continuous variable because the frequency and severity of depressive symptoms were examined, rather than the depressive symptom status.

9.5 Related Concepts Beyond the Scope of this Thesis

This thesis presents new findings which add to the current understanding of the dynamic trajectory of post-stroke depression and the value of patient-reported outcome measures. However, as new findings are discovered, new questions arise. It is important to acknowledge concepts which relate to the key themes and main findings of this thesis, which are important in stroke research and practice – but which are beyond the scope of this thesis. Each of the following concepts, considered beyond the scope of this thesis, are briefly discussed in subsequent sections.

- Treatment and management of post-stroke depression
- Qualitative data to support quantitative findings
- Other constructs associated with post-stroke depression

9.5.1 Treatment and management of post-stroke depression

A key theme of this thesis is post-stroke depression and its trajectory. An important associated topic, which is not explored in this thesis, is the treatment and management of post-stroke depression. The question I am most frequently asked, during discussions and presentations of findings from this thesis, is along the lines of: *"So, once you've screened stroke survivors and identified those experiencing depressive symptoms, what next? How is post-stroke depression treated, and are the treatments effective?"* I recognise the importance of this question. The treatment and management of post-stroke depression is related to the themes of this thesis – and is clearly an important 'next step' which follows on from my research. My research has highlighted that if a stroke survivor meets the validated cut-off score on a screening tool for depression, they should be referred for a diagnostic interview. If depression is subsequently confirmed, this should then lead to treatment and management.

There is considerable research examining the effectiveness of treatments for post-stroke depression, with mixed findings. Broadly, the treatment of post-stroke depression comprises two arms – psychological support and pharmacological treatment. Psychological support includes the provision of counselling with specific evidence-based therapies such as Acceptance and Commitment Therapy (ACT), Cognitive Behavioural Therapy (CBT) and social support interventions such as peer-support and group therapy (Wang et al., 2018; Majumdar & Morris, 2018; Cheung, 2019). Pharmacological treatment includes the use of antidepressant medication, such as Selective Serotonin Reuptake Inhibitors (SSRIs) (Starkstein & Hayhow, 2019; Mortensen & Andersen, 2021). Three recent and related randomised controlled trials: Fluoxetine Or Control Under Supervision (FOCUS) (Dennis et al., 2019); Efficacy of Fluoxetine – a Randomised Controlled Trial in Stroke (EFFECTS) (Lundström et al., 2021); and Assessment of Fluoxetine in

Stroke Recovery Trial (AFFINITY) (Almeida et al., 2021), demonstrated that the SSRI, fluoxetine, given daily, reduced the occurrence of post-stroke depression by 6 months following stroke onset. While on average a positive effect was obtained in these cohorts, current approaches to the treatment of depression following stroke recommend personalised interventions that are effective and safe – rather than the routine prescription of antidepressants for all patients with post-stroke depression (Almeida et al., 2021). While it is recognised that other treatments may be available, further exploration of this topic is beyond the scope of this thesis.

9.5.2 Qualitative data to support quantitative findings

The empirical research studies in this thesis employ quantitative methods to address the research questions. I have been asked if I also conducted qualitative research to further explore my findings. I acknowledge the added value of qualitative information, alongside quantitative findings, but this was beyond scope of my thesis. Qualitative evidence is of particular importance in capturing the individual's perceived experience of post-stroke depression and recovery, which greatly enhances our understanding of these topics. Further, the importance of considering overall recovery in the context of the individual's life following stroke has already been highlighted by qualitative interviews (Dowswell et al., 2000). It would be very informative to explore stroke survivors' individual trajectories of depression over time by undertaking a participatory approach and by using mixed methods – both quantitative and qualitative methods simultaneously.

9.5.3 Suicide by stroke survivors

A comment made during a presentation of my research findings was related to the important topic of suicide by stroke survivors. The gravity of the impact of post-stroke depression is reflected by the presence of suicidal ideation and the occurrence, in some cases, of suicide. Post-stroke depression has been shown to be associated with increased suicidal ideation (Bartoli et al., 2018). Further, the risk of a suicide is 73 per cent higher in stroke survivors, compared to the general population (Vyas et al., 2021). Stroke survivors frequently experience factors associated with suicide – depression, unemployment, social isolation and chronic health conditions (Vyas, et al. 2016). This association between post-stroke depression and suicide, further highlights the importance of screening for depression in stroke survivors.

Chapter 10.

Overall Conclusion

This chapter presents the overall conclusions pertaining to the research findings of this thesis. It reflects on the primary aims and research questions posed in the General Introduction, presented in Chapter 1. This overall conclusions chapter summarises the main findings of this research and highlights their collective importance. Importantly, this chapter highlights how findings from this thesis advance the current literature and provide an opportunity to improve current clinical practice in the management of post-stroke depression. Three main conclusions have been reached; these are highlighted in the following paragraphs.

This thesis has achieved the two primary aims stated in the General Introduction (Chapter 1). The first aim was to explore and characterise the trajectory of post-stroke depression over time. The second aim was to explore the association of post-stroke depressive symptoms and recovery outcomes following stroke. These aims have been achieved by addressing each of the research questions and providing responses based on the findings from Empirical Research Studies 1, 2 and 3 (Chapters 5, 7 and 8), the Review (Chapter 2) and the Perspective Article (Chapter 6).

The main findings of this thesis have been categorised into three key themes. These findings add to the current stroke literature and provide opportunities to improve stroke clinical practice. The key theme relating to *the prevalence and trajectory of post-stroke depression* emerged from the first two main findings. The first main finding is that depression is prevalent among stroke survivors. Both the Review (Chapter 2) and Empirical Research Study 1 (Chapter 5) contributed to this finding. The second main finding is that the trajectory of post-stroke depression is dynamic. Empirical Research Study 1 (Chapter 5) adds evidence for the dynamic trajectory of post-stroke depression among individual stroke survivors. These findings highlight the importance of increasing clinician awareness of post-stroke depression and its dynamic trajectory.

The next key theme, regarding *screening for post-stroke depression*, emerged from the third and fourth main findings. The third main finding is that post-stroke depression is a condition suitable for routine screening. The fourth main finding is that post-stroke depression is a condition that requires screening at repeated intervals. Empirical Research Study 1 (Chapter 5) demonstrates that at 3 months post-stroke, depressive symptoms are not only prevalent, but also are strongly associated with depressive symptoms persisting at 12 months. Empirical Research Study 1 (Chapter 5) and the Perspective Article (Chapter 6) argue that post-stroke depression is a condition that is eminently suitable for routine and repeated screening – which appears to be contrary to current national guidelines. These findings highlight a gap in current Australian stroke

practice, thereby providing an opportunity to improve stroke outcomes by updating these guidelines.

The final key theme, regarding *post-stroke depression and the value of patient perceived recovery outcomes*, emerged from the fifth and sixth main findings. The fifth main finding is that post-stroke depressive symptoms are associated with patient-reported outcomes. The sixth main finding is that the use of patient-reported outcome measures provides important information relating to recovery from stroke. Empirical Research Study 2 (Chapter 7) shows that patient-reported outcome measures appear to capture the impact of depressive symptoms post-stroke. Empirical Research Study 3 (Chapter 8) demonstrates that patient-reported outcome measures also reflect the impact of pre-existing comorbidities in stroke survivors. These findings highlight the value of patient-reported outcome measures in stroke clinical practice. This presents an opportunity to promote the use of patient-reported outcome measures, alongside observer-rated measures, to obtain a more complete picture of overall recovery following stroke.

In conclusion, the findings of this original and sustained dissertation collectively contribute to the current understanding of the trajectory of post-stroke depression and its impact on patient perceived recovery. This thesis provides ideas for future research, and also presents opportunities for improvements in current clinical practice regarding the management of post-stroke depression.

References

Aben, I., Verhey, F., Strik, J., Lousberg, R., Lodder, J., & Honig, A. (2003). A comparative study into the one year cumulative incidence of depression after stroke and myocardial infarction. *Journal of Neurology, Neurosurgery and Psychiatry, 74*(5), 581–585. https://doi.org/10.1136/jnnp.74.5.581

Adamson, J., Beswick, A., & Ebrahim, S. (2004). Is stroke the most common cause of disability? *Journal of Stroke and Cerebrovascular Diseases, 13*(4), 171–177. https://doi.org/10.1016/j.jstrokecerebrovasdis.2004.06.003

Aho, K., Harmsen, P., Hatano, S., Marquardsen, J., Smirnov, V. E., & Strasser, T. (1980). Cerebrovascular disease in the community: Results of a WHO collaborative study. *Bulletin of the World Health Organization, 58*(1), 113–130.

Alexander, T., & Wilz, G. (2010). Family caregivers: Gender differences in adjustment to stroke survivors' mental changes. *Rehabilitation Psychology, 55*(2), 159–169. https://doi.org/10.1037/a0019253

Alexopoulos, G. S., Abrams, R. C., Young, R. C., & Shamoian, C. A. (1988). Cornell scale for depression in dementia. *Biological Psychiatry*, *23*(3), 271–284. https://doi.org/10.1016/0006-3223(88)90038-8

Allan, L. M., Rowan, E. N., Thomas, A. J., Polvikoski, T. M., O'Brien, J. T., & Kalaria, R. N. (2013). Long-term incidence of depression and predictors of depressive symptoms in older stroke survivors. *British Journal of Psychiatry, 203*(6), 453–460. https://doi.org/10.1192/bjp.bp.113.128355

Almeida, O. P., Hankey, G. J., Ford, A., Etherton-Beer, C., Flicker, L., Hackett, M., & Assessment of Fluoxetine in Stroke Recovery (AFFINITY) Trial Collaboration. (2021). Depression outcomes among patients treated with fluoxetine for stroke recovery: the AFFINITY randomized clinical trial. *The Journal of the American Medical Association Neurology, 78*(9), 1072-1079. https://doi.org/10.1001/jamaneurol.2021.2418

Amaricai, E., & Poenaru, D. V. (2016). The post-stroke depression and its impact on functioning in young and adult stroke patients of a rehabilitation unit. *Journal of Mental Health, 25*(2), 137-141. https://doi.org/10.3109/09638237.2015.1022251

American Psychiatric Association. (2013a). *Diagnostic and statistical manual of mental disorders (5th ed.): DSM-5*. American Psychiatric Publishing. https://doi.org/10.1176/appi.books.9780890425596

American Psychiatric Association. (2013b). *Highlights of changes from DSM-IV-TR to DSM-5.* https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM_Changes_from_DSM-IV-TR_-to_DSM-5.pdf

American Psychological Association. (2019). *Publication manual of the American Psychological Association (7th ed.).* Washington, D.C. American Psychological Association.

Andrew, N. E., Kilkenny, M., Naylor, R., Purvis, T., Lalor, E., Moloczij, N., & Cadilhac, D. A. (2014). Understanding long-term unmet needs in Australian survivors of stroke. *International Journal of Stroke, 9*(SA100), 106–112. https://doi.org/10.1111/ijs.12325

Armstrong, R. A. (2014). When to use the Bonferroni correction. *Ophthalmic and Physiological Optics*, *34*(5), 502–508. https://doi.org/10.1111/opo.12131

Aron, A. W., Staff, I., Fortunato, G., & McCullough, L. D. (2015). Prestroke living situation and depression contribute to initial stroke severity and stroke Recovery. *Journal of Stroke and Cerebrovascular Diseases, 24*(2), 492–499. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.09.024

Arwert, H. J., Schults, M., Meesters, J., Wolterbeek, R., Boiten, J., & Vliet Vlieland, T. (2017). Return to work 2-5 years after stroke: A cross sectional study in a hospital-based population. *Journal of Occupational Rehabilitation, 27*(2), 239–246. https://doi.org/10.1007/s10926-016-9651-4

Astuti, P., Kusnanto, K., & Dwi Novitasari, F. (2020). Depression and functional disability in stroke patients. *Journal of Public Health Research, 9*:1835, 169-171 https://doi.org/10.4081/jphr.2020.1835

Ayerbe, L., Ayis, S., Crichton, S., Wolfe, C. D. A., & Rudd, A. G. (2013b). The natural history of depression up to 15 years after stroke. *Stroke, 44*(4), 1105–1110. https://doi.org/10.1161/strokeaha.111.679340

Ayerbe, L., Ayis, S., Crichton, S., Wolfe, C. D. A., & Rudd, A. G. (2013c). The long-term outcomes of depression up to 10 years after stroke; the South London Stroke Register. Journal of Neurology, *Neurosurgery and Psychiatry, 85*(5), 514–521. https://doi.org/10.1136/jnnp-2013 306448

Ayerbe, L., Ayis, S., Wolfe, C. D. A., & Rudd, A. G. (2013a). Natural history, predictors and outcomes of depression after stroke: Systematic review and meta-analysis. *The British Journal of Psychiatry, 202*(1), 14–21. https://doi.org/10.1192/bjp.bp.111.107664

Baccaro, A., Wang, Y. P., Brunoni, A. R., Candido, M., Conforto, A. B., da Costa Leite, C., Lotufo, P. A., Benseñor, I. M., & Goulart, A. C. (2019). Does stroke laterality predict major depression and cognitive impairment after stroke? Two-year prospective evaluation in the EMMA study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *94*, 109639. https://doi.org/10.1016/j.pnpbp.2019.109639

Bacher, Y., Korner-Bitensky, N., Mayo, N., Becker, R., & Coopersmith, H. (1990). A longitudinal study of depression among stroke patients participating in a rehabilitation program. *Canadian Journal of Rehabilitation, 4*(1), 27-37. https://doi.org/10.1177/026921559000400105

Bae, K., Kang, H., Kim, J., Kim, S., Kim, J., Park, M., Cho, K., & Kim, J. (2019). Associations of white matter hyperintensities with poststroke depression: A 1-year longitudinal study. *International Journal of Geriatric Psychiatry, 34*(1), 162–168. https://doi.org/10.1002/gps.5005

Banks, J. L., & Marotta, C. A. (2007). Outcomes validity and reliability of the modified Rankin scale: Implications for stroke clinical trials. *Stroke, 38*(3), 1091–1096. https://doi.org/10.1161/01.str.0000258355.23810.c6

Bar, B., & Hemphill, J. C. (2011). Charlson comorbidity index adjustment in intracerebral hemorrhage. *Stroke, 42*(10), 2944–2946. https://doi.org/10.1161/strokeaha.111.617639

Barker-Collo, S., Krishnamurthi, R., Feigin, V., Jones, A., Theadom, A., Barber, P. A., Starkey, N., McPherson, K., Rush, E., & Bennett, D. (2016). Neuropsychological outcome and its predictors across the first year after ischaemic stroke. *Brain Impairment, 17*(2), 111–122. https://doi.org/10.1017/brimp.2016.17

Barrett, A. M. (2010). Rose-colored answers: Neuropsychological deficits and patient-reported outcomes after stroke. *Behavioural Neurology, 22*(1–2), 17–23. https://doi.org/10.1155/2010/628257

Bartoli, F., di Brita, C., Crocamo, C., Clerici, M., & Carrà, G. (2018). Early post-stroke depression and mortality: Meta-analysis and meta-regression. *Frontiers in Psychiatry, 9*. https://doi.org/10.3389/fpsyt.2018.00530

Beck, A. T. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*(6), 561. https://doi.org/10.1001/archpsyc.1961.01710120031004

Berg, A., Palomäki, H., Lehtihalmes, M., Lönnqvist, J., & Kaste, M. (2003). Poststroke depression: An 18-month follow-up. *Stroke, 34*(1), 138–143. https://doi.org/10.1161/01.str.0000048149.84268.07

Berlowitz, D. R., Hoenig, H., Cowper, D. C., Duncan, P. W., & Vogel, W. B. (2008). Impact of comorbidities on stroke rehabilitation outcomes: Does the method matter? *Archives of Physical Medicine and Rehabilitation, 89*(10), 1903–1906. https://doi.org/10.1016/j.apmr.2008.03.024

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

Bonita, R., & Beaglehole, R. (1988). Recovery of motor function after stroke. *Stroke, 19*(12), 1497–1500. https://doi.org/10.1161/01.str.19.12.1497

Bour, A., Rasquin, S., Aben, I., Boreas, A., Limburg, M., & Verhey, F. (2010). A one-year follow-up study into the course of depression after stroke. *The Journal of Nutrition, Health and Aging, 14*(6), 488–493. https://doi.org/10.1007/s12603-010-0033-x

Breen, S., Cadilhac, D. A., Lannin, N. A., Kim, J., Dalli L., Anderson, C. S., Kilkenny, M., Faux, S., Dewey, H., Hill, K, Donnan, G., Grimley, R., Campbell, B., Mitchell, P., Middleton, S., on behalf of the AuSCR Consortium. (2020). *The Australian Stroke Clinical Registry Annual Report 2019 Volume 1: Acute Care Provision*. The Florey Institute of Neuroscience and Mental Health; December 2020, Report No. 11, 53 pages. https://auscr.com.au/about/annual-reports/

Brennan, A., Worrall, L., & McKenna, K. (2005). The relationship between specific features of aphasia-friendly written material and comprehension of written material for people with aphasia: An exploratory study. *Aphasiology, 19*(8), 693–711. https://doi.org/10.1080/02687030444000958

Breusch, T. S., & Pagan, A. R. (1979). A simple test for heteroscedasticity and random coefficient variation. *Econometrica, 47*(5), 1287-1294. https://doi.org/10.2307/1911963

Brodaty, H., Liu, Z., Withall, A., & Sachdev, P. S. (2013). The longitudinal course of post stroke apathy over five years. *The Journal of Neuropsychiatry and Clinical Neurosciences, 25*(4), 283–291. https://doi.org/10.1176/appi.neuropsych.12040080

Brodaty, H., Withall, A., Altendorf, A., & Sachdev, P. S. (2007). Rates of depression at 3 and 15 months poststroke and their relationship with cognitive decline: The Sydney Stroke Study. *The American Journal of Geriatric Psychiatry, 15*(6), 477–486. https://doi.org/10.1097/jgp.0b013e3180590bca

Brott, T., Adams, H. P., Jr, Olinger, C. P., Marler, J. R., Barsan, W. G., Biller, J., Spilker, J., Holleran, R., Eberle, R., & Hertzberg, V. (1989). Measurements of acute cerebral infarction: A clinical examination scale. *Stroke, 20*(7), 864–870. https://doi.org/10.1161/01.str.20.7.864

Bushnell, C. D., Reeves, M. J., Zhao, X., Pan, W., Prvu-Bettger, J., Zimmer, L., Olson, D., & Peterson, E. (2014). Sex differences in quality of life after ischemic stroke. *Neurology, 82*(11), 922–931. https://doi.org/10.1212/wnl.0000000000000208

Cadilhac, D. A., Lannin N. A., Kim J., Anderson C. S., Kilkenny, M., Shehata, S., Grabsch, B., Levi, C., Faux, S., Dewey, H., Hill, K., Donnan, G., Hand, P., Grimley, R., Middleton, S., on behalf of the AuSCR Consortium. (2016). *The Australian Stroke Clinical Registry Annual Report 2016.* Florey Institute of Neuroscience and Mental Health; December 2017, Report No. 8, 53 pages. https://auscr.com.au/about/annual-reports/

Cai, W., Mueller, C., Li, Y. J., Shen, W. D., & Stewart, R. (2019). Post stroke depression and risk of stroke recurrence and mortality: A systematic review and meta-analysis. *Ageing Research Reviews, 50*, 102–109. https://doi.org/10.1016/j.arr.2019.01.013

Campbell, B. (2016). Thrombolysis and Thrombectomy for Acute Ischemic Stroke: Strengths and Synergies. *Seminars in Thrombosis and Hemostasis, 43*(02), 185–190. https://doi.org/10.1055/s0036-1585078

Campbell, B., De Silva, D. A., Macleod, M. R., Coutts, S. B., Schwamm, L. H., Davis, S. M., & Donnan, G. A. (2019). Ischaemic stroke. *Nature Reviews. Disease Primers, 5*(1), 70. https://doi.org/10.1038/s41572-019-0118-8

Carey, L. M., & Seitz, R. J. (2007). Functional neuroimaging in stroke recovery and neurorehabilitation: Conceptual issues and perspectives. *International Journal of Stroke, 2*(4), 245–264. https://doi.org/10.1111/j.1747-4949.2007.00164.x

Carey, L. M., Crewther, S., Salvado, O., Lindén, T., Connelly, A., Wilson, W., Howells, D. W., Churilov, L., Ma, H., Tse, T., Rose, S., Palmer, S., Bougeat, P., Campbell, B. C. V., Christensen, S., Macaulay, S. L., Favaloro, J., Collins, V. O., Mcbride, S., … Donnan, G. A. (2015). Stroke imAging pRevention and Treatment (START): A longitudinal stroke cohort study: Clinical trials protocol. *International Journal of Stroke, 10*(4), 636–644. https://doi.org/10.1111/ijs.12190

Carod-Artal, F. J., & Egido, J. A. (2009). Quality of life after stroke: The importance of a good recovery. *Cerebrovascular Diseases, 27*(1), 204–214. https://doi.org/10.1159/000200461

Carod-Artal, F. J., Coral, L. F., Trizotto, D. S., & Moreira, C. M. (2008). The Stroke Impact Scale 3.0. *Stroke, 39*(9), 2477–2484. https://doi.org/10.1161/strokeaha.107.513671

Castiglia, S. F., Galeoto, G., Lauta, A., Palumbo, A., Tirinelli, F., Viselli, F., Santilli, V., & Sacchetti, M. L. (2017). The culturally adapted Italian version of the Barthel Index (IcaBI): Assessment of structural validity, inter-rater reliability and responsiveness to clinically relevant improvements in patients admitted to inpatient rehabilitation centers. *Functional Neurology, 22*(4), 221–228. https://doi.org/10.11138/fneur/2017.32.4.221

Centres for Disease Control and Prevention (2012, May 18). *Principles of epidemiology in public health practice, (3rd ed.). An introduction to applied epidemiology and biostatistics, lesson 3: Measures of risk.* https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section2.html

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases, 40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Chemerinski, E., Robinson, R. G., & Kosier, J. T. (2001). Improved recovery in activities of daily living associated with remission of poststroke depression. *Stroke, 32*(1), 113–117. https://doi.org/10.1161/01.str.32.1.113

Cheung, R. T. (2014). A systematic approach to the definition of stroke. *Austin Journal of Cerebrovascular Disease and Stroke, 1*(5), 1024. https://doi.org/10722/214339

Cheung, V. K. L. (2019). The effectiveness of cognitive behavioral therapy for people with depression following stroke: A systematic review and meta-analysis. *International Journal of Psychotherapy, Counselling and Psychiatry: Theory Research & Clinical Practice, 4*(3). https://doi.org/10.35996/1234/4/cbtdepressionstroke

Clark, M. S., & Smith, D. S. (1998). The effects of depression and abnormal illness behaviour on outcome following rehabilitation from stroke. *Clinical Rehabilitation, 12*(1), 73–80. https://doi.org/10.1191/026921598669567216

Cochrane Collaboration (2011, March). *Cochrane Handbook for Systematic Reviews of Interventions. 7.7 Extracting study results and converting to the desired format.* https://handbook-5-1.cochrane.org/chapter_7/7_7_extracting_study_results_and_converting_to_the_desired.htm

Colquhoun, D. M., Bunker, S. J., Clarke, D. M., Glozier, N., Hare, D. L., Hickie, I. B., Tatoulis, J., Thompson, D. R., Tofler, G. H., Wilson, A., & Branagan, M. G. (2013). Screening, referral and treatment for depression in patients with coronary heart disease. *Medical Journal of Australia, 198*(9), 483–484. https://doi.org/10.5694/mja13.10153

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

Coupland, A. P., Thapar, A., Qureshi, M. I., Jenkins, H., & Davies, A. H. (2017). The definition of stroke. *Journal of the Royal Society of Medicine, 110*(1), 9–12. https://doi.org/10.1177/0141076816680121

Cramm, J. M., & Nieboer, A. P. (2018). Validation of an instrument for the assessment of patient centred care among patients with multimorbidity in the primary care setting: The 36-item patient centred primary care instrument. *BioMedical Central Family Practice, 19*(1). https://doi.org/10.1186/s12875-018-0832-4

Crichton, S. L., Bray, B. D., McKevitt, C., Rudd, A. G., & Wolfe, C. D. A. (2016). Patient outcomes up to 15 years after stroke: Survival, disability, quality of life, cognition and mental health. *Journal of Neurology, Neurosurgery and Psychiatry, 87*(10), 1091–1098. https://doi.org/10.1136/jnnp-2016-313361

Crowley, D., & Andrews, L. (2018). The longitudinal relationship between acceptance and anxiety and depression in people who have had a stroke. *Aging and Mental Health, 22*(10), 1321-1328. https://doi.org/10.1080/13607863.2017.1348478

Cumming, T. B., Churilov, L., Skoog, I., Blomstrand, C., & Linden, T. (2010). Little evidence for different phenomenology in poststroke depression. *Acta Psychiatrica Scandinavica, 121*(6), 424 430. https://doi.org/10.1111/j.1600-0447.2010.01558.x

Dafer, R. M., Rao, M., Shareef, A., & Sharma, A. (2008). Poststroke depression. *Topics in Stroke Rehabilitation, 15*(1), 13–21. https://doi.org/10.1310/tsr1501-13

Das, J., & Rajanikant, G.K. (2018). Post stroke depression: The sequelae of cerebral stroke. *Neuroscience and Biobehavioral Reviews, 90,* 104–114. https://doi.org/10.1016/j.neubiorev.2018.04.005

Davino, C., Furno, M., & Vistocco, D. (2014). Quantile regression: Theory and applications (1st ed.). John Wiley & Sons, Ltd. ISBN: 978-1-119-97528-1

de Coster, L., Leentjens, A. F., Lodder, J., & Verhey, F. R. (2005). The sensitivity of somatic symptoms in post-stroke depression: A discriminant analytic approach. *International Journal of Geriatric Psychiatry, 20*(4), 358–362. https://doi.org/10.1002/gps.1290

De Ryck, A., Fransen, E., Brouns, R., Geurden, M., Peij, D., Mariën, P., de Deyn, P., & Engelborghs, S. (2014). Poststroke depression and its multifactorial nature: Results from a prospective longitudinal study. *Journal of the Neurological Sciences, 347*(1–2), 159–166. https://doi.org/10.1016/j.jns.2014.09.038

De Wit, L., Putman, K., Baert, I., Lincoln, N. B., Angst, F., Beyens, H., Bogaerts, K., Brinkmann, N., Connell, L., Dejaeger, E., de Weerdt, W., Jenni, W., Kaske, C., Komárek, A., Lesaffre, E., Leys, M., Louckx, F., Schuback, B., Schupp, W., . . . Feys, H. (2008). Anxiety and depression in the first six months after stroke. A longitudinal multicentre study. *Disability and Rehabilitation, 30*(24), 1858–1866. https://doi.org/10.1080/09638280701708736

Deloitte Access Economics. (2020a) *No postcode untouched – stroke in Australia 2020*. https://strokefoundation.org.au/What-we-do/Research/No-Postcode-Untouched

Deloitte Access Economics (2020b). *The economic impact of stroke in Australia.* https://strokefoundation.org.au/News/2020/11/04/02/57/No%20Postcode%20Untouched

Dennis, M., Forbes, J., Grahan, C., Hackett, M., Hankey, G. J., House, A., Lewis, S., Lundström, E., Sandercock, P., Mead, G., & FOCUS Trial Collaboration. (2019). Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. *Lancet, 19*(393), 265-274. https://doi.org/10.1016/S0140-6736(18)32823-X

Dong, L., Williams, L. S., Brown, D. L., Case, E., Morgenstern, L. B., & Lisabeth, L. D. (2021). Prevalence and course of depression during the first year after mild to moderate stroke. *Journal of the American Heart Association, 10(*13). https://doi.org/10.1161/jaha.120.020494

dos Santos, E. B., Rodrigues, R. A. P., Fhon, J. R. S., & Haas, V. J. (2018). Changes and predictors of psychological stress among elderly stroke survivors 6 months after hospital discharge. *Stress and Health, 34*(3), 359–366. https://doi.org/10.1002/smi.2791

Douven, E., Staals, J., Schievink, S. H., van Oostenbrugge, R. J., Verhey, F. R., Wetzels Meertens, S., Köhler, S., & Aalten, P. (2018). Personality traits and course of symptoms of depression and apathy after stroke: Results of the CASPER study. *Journal of Psychosomatic Research, 111*, 69–75. https://doi.org/10.1016/j.jpsychores.2018.05.010

Dowswell, G., Lawler, J., Dowswell, T., Young, J., Forster, A., & Hearn, J. (2000). Investigating recovery from stroke: A qualitative study. *Journal of Clinical Nursing, 9*(4), 507–515. https://doi.org/10.1046/j.1365-2702.2000.00411.x

Duncan, P. W., Lai, S. M., & Keighley, J. (2000). Defining post-stroke recovery: Implications for design and interpretation of drug trials. *Neuropharmacology, 39*(5), 835–841. https://doi.org/10.1016/s0028-3908(00)00003-4

Duncan, P. W., B Bode, R. K., Lai, S. M., Perera, S., & Glycine Antagonist in Neuroprotection Americans Investigators (2003a). Rasch analysis of a new stroke-specific outcome scale: The Stroke Impact Scale. *Archives of Physical Medicine and Rehabilitation, 84*(7), 950–963. https://doi.org/10.1016/s0003-9993(03)00035-2

Duncan, P., Lai, S. M., Bode, R.K., Perera, S., & DeRosa, J., & Glycine Antagonist in Neuroprotection Americans Investigators (2003b). Stroke Impact Scale-16: A brief assessment of physical function. *Neurology, 60*(2), 291–296. https://doi.org/10.1212/01.wnl.0000041493.65665.d6

Duncan, P. W. (2013). Outcome measures in stroke rehabilitation. *Neurological Rehabilitation*, 105–111. https://doi.org/10.1016/b978-0-444-52901-5.00009-5

Edwards, D. F., Hahn, M., Baum, C., & Dromerick, A. W. (2006). The impact of mild stroke on meaningful activity and life satisfaction. *Journal of Stroke and Cerebrovascular Diseases, 15*(4), 151–157. https://doi.org/10.1016/j.jstrokecerebrovasdis.2006.04.001

El Husseini, N., Goldstein, L. B., Peterson, E. D., Zhao, X., Olson, D. M., Williams, J. W., Bushnell, C., & Laskowitz, D. T. (2017). Depression status is associated with functional decline over 1-year following acute stroke. *Journal of Stroke and Cerebrovascular Diseases*, *26*(7), 1393–1399. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.03.026

Eriksen, S., Gay, C. L., & Lerdal, A. (2015). Acute phase factors associated with the course of depression during the first 18 months after first-ever stroke. *Disability and Rehabilitation, 38(*1), 30–35. https://doi.org/10.3109/09638288.2015.1009181

Fang, J., & Cheng, Q. (2009). Etiological mechanisms of post-stroke depression: A review. *Neurological Research, 31*(9), 904–909. https://doi.org/10.1179/174313209x385752

Farrell, B., Godwin, J., Richards, S., & Warlow, C. (1991). The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: Final results. *Journal of Neurology, Neurosurgery, and Psychiatry, 54*(12), 1044–1054. https://doi.org/10.1136/jnnp.54.12.1044

Feigin, V. L., Nguyen, G., Cercy, K., Johnson, C. O., Alam, T., Parmar, P. G., Abajobir, A. A., Abate, K. H., Abd-Allah, F., Abejie, A. N., Abyu, G. Y., Ademi, Z., Agarwal, G., Ahmed, M. B., Akinyemi, R. O., Al-Raddadi, R., Aminde, L. N., Amlie-Lefond, C., Ansari, H., … Roth, G. A. (2018). Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. *The New England Journal of Medicine, 379*(25), 2429-2437. https://doi.org/10.1056/NEJMoa1804492

Fischer, U., Arnold, M., Nedeltchev, K., Schoenenberger, R., Kappeler, L., Hollinger, P., Schroth, G., Ballinari, P., & Mattle, H. (2006). Impact of comorbidity on ischemic stroke outcome. *Acta Neurologica Scandinavica, 113*(2), 108–113. https://doi.org/10.1111/j.1600-0404.2005.00551.x

Folstein, M. F., Maiberger, R., & Mchugh, P. R. (1977). Mood disorder as a specific complication of stroke. *Journal of Neurology, Neurosurgery & Psychiatry, 40*(10), 1018–1020. https://doi.org/10.1136/jnnp.40.10.1018

Fuentes, B., Ortiz, X., SanJose, B., Frank, A., & Díez-Tejedor, E. (2009). Post-stroke depression: Can we predict its development from the acute stroke phase? *Acta Neurologica Scandinavica, 120*(3), 150–156. https://doi.org/10.1111/j.1600-0404.2008.01139.x

Gaete, J. M., & Bogousslavsky, J. (2008). Post-stroke depression. *Expert Review of Neurotherapeutics, 8*(1), 75–92. https://doi.org/10.1586/14737175.8.1.75

Gainotti, G. (2001). Relation between depression after stroke, antidepressant therapy, and functional recovery. *Journal of Neurology, Neurosurgery and Psychiatry, 71*(2), 258–261. https://doi.org/10.1136/jnnp.71.2.258

Gilbody, S., Sheldon, T., & House, A. (2008). Screening and case-finding instruments for depression: A meta-analysis. *Canadian Medical Association Journal, 178*(8), 997–1003. https://doi.org/10.1503/cmaj.070281

Gillen, R., Tennen, H., McKee, T. E., Gernert-Dott, P., & Affleck, G. (2001). Depressive symptoms and history of depression predict rehabilitation efficiency in stroke patients. *Archives of Physical Medicine and Rehabilitation, 82*(12), 1645–1649. https://doi.org/10.1053/apmr.2001.26249

Gold, S. M., Köhler-Forsberg, O., Moss-Morris, R., Mehnert, A., Jaime Miranda, J., Bullinger, M., Steptoe, A., Whooley, M. A., & Otte, C. Comorbid depression in medical diseases. (2020). *Nature Reviews Disease Primers, 6*(1). https://doi.org/10.1038/s41572-020-0211-z

Goldstein, L. B., Samsa, G. P., Matchar, D. B., & Horner, R. D. (2004). Charlson index comorbidity adjustment for ischemic stroke outcome studies. *Stroke, 35*(8), 1941–1945. https://doi.org/10.1161/01.str.0000135225.80898.1c

Götze, H., Taubenheim, S., Dietz, A., Lordick, F., & Mehnert-Theuerkauf, A. (2019). Fear of cancer recurrence across the survivorship trajectory: Results from a survey of adult long-term cancer survivors. *Psycho-oncology, 28*(10), 2033–2041. https://doi.org/10.1002/pon.5188

Goyder, E., Barratt, A., & Irwig, L. (2000). Telling people about screening programmes and screening test results: How can we do it better? *Journal of Medical Screening, 7*(3), 123–126. https://doi.org/10.1136/jms.7.3.123

Gubrium, J. F., Rittman, M. R., Williams, C., Young, M. E., & Boylstein, C. A. (2003). Benchmarking as everyday functional assessment in stroke recovery. *The Journals of Gerontology. Series B, 58*(4), S203–S211. https://doi.org/10.1093/geronb/58.4.s203

Guidetti, S., Ytterberg, C., Ekstam, L., Johansson, U., & Eriksson, G. (2014). Changes in the impact of stroke between 3 and 12 months post-stroke, assessed with the Stroke Impact Scale. *Journal of Rehabilitation Medicine, 46*(10), 963–968. https://doi.org/10.2340/16501977-1865

Guo, J., Wang, J., Sun, W., & Liu, X. (2021). The advances of post-stroke depression: 2021 update. Published. *Journal of Neurology.* https://doi.org/10.1007/s00415-021-10597-4

Guo, Y. E., Togher, L., Power, E., Heard, R., Luo, N., Yap, P., & Koh, G. C. H. (2017). Sensitivity to change and responsiveness of the stroke and aphasia quality-of-life scale (SAQOL) in a Singapore stroke population. *Aphasiology, 31*(4), 427–446. https://doi.org/10.1080/02687038.2016.1261269

Guthrie, B., Payne, K., Alderson, P., McMurdo, M. E. T., & Mercer, S. W. (2012). Adapting clinical guidelines to take account of multimorbidity. *British Medical Journal, 345*, e6341. https://doi.org/10.1136/bmj.e6341

Habibzadeh, F., & Habibzadeh, P. (2020). The mean prevalence. *Epidemiologic Methods, 9*(1). https://doi.org/10.1515/em-2019-0033

Hackett, M. L., & Pickles, K. (2014). Part I: Frequency of depression after stroke: An updated systematic review and meta-analysis of observational studies. *International Journal of Stroke, 9*(8), 1017–1025. https://doi.org/10.1111/ijs.12357

Hackett, M. L., Yapa, C., Parag, V., & Anderson, C. S. (2005). Frequency of depression after stroke. *Stroke, 36*(6), 1330–1340. https://doi.org/10.1161/01.str.0000165928.19135.35

Hadidi, N., Lindquist, R., Treat-Jacobson, D., & Savik, K. (2011). Natural patterns of change in poststroke depressive symptoms and function. *Western Journal of Nursing Research, 33*(4), 522–539. https://doi.org/10.1177/0193945910382426

Haley, W. E., Roth, D. L., Kissela, B., Perkins, M., & Howard, G. (2011). Quality of life after stroke: A prospective longitudinal study. *Quality of Life Research, 20*(6), 799–806. https://doi.org/10.1007/s11136-010-9810-6

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry, 23*(1), 56–62. https://doi.org/10.1136/jnnp.23.1.56

Hamza, A. M., Al-Sadat, N., Loh, S. Y., & Jahan, N. K. (2014). Predictors of poststroke health related quality of life in Nigerian stroke survivors: A 1-Year Follow-Up Study. *BioMed Research International,* 1–7. https://doi.org/10.1155/2014/350281

Hannah, D., Lindholm, B., & Maisch, L. (2014). Certain uncertainty: Life after stroke from the patient's perspective. *Circulation: Cardiovascular Quality and Outcomes, 7*(6), 968–969. https://doi.org/10.1161/circoutcomes.114.001315

Heart and Stroke Foundation of Canada. (2018). *Canadian Stroke Best Practices. Mood Cognition and Fatigue following Stroke.* https://www.strokebestpractices.ca/recommendations/mood-cognition-and-fatigue-following-stroke/post-stroke-depression.

Herrmann, M., & Wallesch, C., W. (1993). Depressive changes in stroke patients. *Disability and Rehabilitation, 15*(2), 55–66. https://doi.org/10.3109/09638289309165873

Hjollund, N. H. I. (2017). Individual prognosis of symptom burden and functioning in chronic diseases: A generic method based on patient-reported outcome (PRO) measures. *Journal of Medical Internet Research, 19*(8), e278. https://doi.org/10.2196/jmir.8111

Hommel, M., Trabucco-Miguel, S., Joray, S., Naegele, B., Gonnet, N., & Jaillard, A. (2009). Social dysfunctioning after mild to moderate first-ever stroke at vocational age. *Journal of Neurology, Neurosurgery & Psychiatry, 80*(4), 371–375. https://doi.org/10.1136/jnnp.2008.157875

Horgan, N. F., O'Regan, M., Cunningham, C. J., & Finn, A. M. (2009). Recovery after stroke: A 1 year profile. *Disability and Rehabilitation, 31*(10), 831–839. https://doi.org/10.1080/09638280802355072

Hu, R., Wang, X., Liu, Z., Hou, J., Liu, Y., Tu, J., Jia, M., Liu, Y., & Zhou, H. (2020). Stigma, depression, and post-traumatic growth among Chinese stroke survivors: A longitudinal study examining patterns and correlations. *Topics in Stroke Rehabilitation*, 1–14. https://doi.org/10.1080/10749357.2020.1864965

Hung, J. W., Chang, K. C., Huang, Y. C., Chen, J. H., Liao, L. N., Lin, C. J., & Chuo, C. Y. (2012). Factors associated with strain in informal caregivers of stroke patients. *Biomedical Journal, 35*(5), 392. https://doi.org/10.4103/2319-4170.105479

Iacoboni, M., Padovani, A., di Piero, V., & Lenzi, G. L. (1995). Post-stroke depression: Relationships with morphological damage and cognition over time. *The Italian Journal of Neurological Sciences, 16*(3), 209–216. https://doi.org/10.1007/bf02282991

Jenkinson, C., Fitzpatrick, R., Crocker, H., & Peters, M. (2013). The Stroke Impact Scale. Validation in a UK setting and development of a SIS short form and SIS index. *Stroke, 44*(9), 2532–2535. https://doi.org/10.1161/strokeaha.113.001847

Jiménez Caballero, P. E., López Espuela, F., Portilla Cuenca, J. C., Ramírez Moreno, J. M., Pedrera Zamorano, J. D., & Casado Naranjo, I. (2013). Charlson Comorbidity Index in ischemic stroke and intracerebral hemorrhage as predictor of mortality and functional outcome after 6 months. *Journal of Stroke and Cerebrovascular Diseases, 22*(7), e214–e218. https://doi.org/10.1016/j.jstrokecerebrovasdis.2012.11.014

Johnson, C. O., Nguyen, M., Roth, G. A., Nichols, E., Alam, T., Abate, D., Abd-Allah, F., Abdelalim, A., Abraha, H. N., Abu-Rmeileh, N. M., Adebayo, O. M., Adeoye, A. M., Agarwal, G., Agrawal, S., Aichour, A. N., Aichour, M. T. E., Alahdab, F., Ali, R. … Murray, C. J. L. (2019). Global, regional, and national burden of stroke, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Neurology, 18*(5), 439-458. https://doi.org/10.1016/S1474-4422(19)30034-1

Jones, F., Mandy, A., & Partridge, C. (2008). Reasons for recovery after stroke: A perspective based on personal experience. *Disability and Rehabilitation*, *30*(7), 507–516. https://doi.org/10.1080/09638280701355561

Jones, A., Smakowski, A., O'Connell, N., Chalder, T., & David, A. S. (2020). Functional stroke symptoms: A prospective observational case series. *Journal of Psychosomatic Research, 132*, 109972. https://doi.org/10.1016/j.jpsychores.2020.109972

Dar, S. K., Venigalla, H., Khan, A. M., Ahmed, R., Mekala, H. M., Zain, H., & Shagufta, S. (2017). Post stroke depression frequently overlooked, undiagnosed, untreated. *Neuropsychiatry, 7*(6), 906-919. https://doi.org/10.4172/neuropsychiatry.1000296

Kang, H. J., Stewart, R., Kim, J. M., Jang, J. E., Kim, S. Y., Bae, K. Y., Kim, S. W., Shin, I. S., Park, M. S., Cho, K. H., & Yoon, J. S. (2013). Comparative validity of depression assessment scales for screening poststroke depression. *Journal of Affective Disorders, 147*(1–3), 186–191. https://doi.org/10.1016/j.jad.2012.10.035

Kapoor, A., Lanctot, K. L., Bayley, M., Herrmann, N., Murray, B. J., & Swartz, R. H. (2019). Screening for post-stroke depression and cognitive impairment at baseline predicts long-term patient-centered outcomes after stroke. *Journal of Geriatric Psychiatry and Neurology, 32*(1), 40–48. https://doi.org/10.1177/0891988718819859

Katan, M., & Luft, A. (2018). Global burden of stroke. *Seminars in Neurology, 38*(2), 208–211. https://doi.org/10.1055/s-0038-1649503

Katzan, I. L., Thompson, N. R., Lapin, B., & Uchino, K. (2017). Added value of patient reported outcome measures in stroke clinical practice. *Journal of the American Heart Association, 6*(7), e005356. https://doi.org/10.1161/jaha.116.005356

Katzenellenbogen, J.M., Vos, T., Somerford, P., Begg, S., Semmens, J.B., & Codde, J.P. (2011). Burden of stroke in Indigenous Western Australians: a study using data linkage. *Stroke, 42*(6), 1515-1521. https://doi.org/10.1161/STROKEAHA.110.601799

Kauhanen, M. L., Korpelainen, J., Hiltunen, P., Määttä, R., Mononen, H., Brusin, E., Sotaniemi, K., & Myllylä, V. (2000). Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovascular Diseases, 10*(6), 455–461. https://doi.org/10.1159/000016107

Kawasaki, M., & Hoshiyama, M. (2020). Apathy and depression during the recovery stage after stroke. *International Journal of Therapy and Rehabilitation, 27*(5), 1–12. https://doi.org/10.12968/ijtr.2018.0070

Keith, R. A., Granger, C. V., Hamilton, B. B., & Sherwin, F. S. (1987). The functional independence measure: A new tool for rehabilitation. *Advances in Clinical Rehabilitation, 1*, 6–18. PMID: 3503663

Kessler, R. C., & Ustün, T. B. (2004). The World Mental Health (WMH) survey initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *International Journal of Methods in Psychiatric Research, 13*(2), 93–121. https://doi.org/10.1002/mpr.168

Khan F. (2004). Poststroke depression. *Australian Family Physician, 33*(10), 831–834. PMID: 15532160

Kilkenny, M. F., Harris, D. M., Ritchie, E. A., Price, C., & Cadillac, D.A. (2013). Hospital management and outcomes of stroke in indigenous Australians: evidence from the 2009 acute care national stroke audit. *International Journal of Stroke, 8*(3), 164-171. https://doi.org/10.1111/j.1747-4949.2011.00717.x

Kim, E., & Kim, A. R. (2016). Longitudinal change and associated factors of post-stroke depression: A prospective follow-up study. *Archives of Physical Medicine and Rehabilitation, 97*(10), e109. https://doi.org/10.1016/j.apmr.2016.08.340

Kim, J. H. (2019). Multicollinearity and misleading statistical results. *Korean Journal of Anesthesiology, 72*(6), 558–569. https://doi.org/10.4097/kja.19087

Kim, J. M., Stewart, R., Kang, H. J., Bae, K. Y., Kim, S. W., Shin, I. S., Kim, J. T., Park, M. S., Cho, K. H., & Yoon, J. S. (2014). A prospective study of statin use and poststroke depression. *Journal of Clinical Psychopharmacology, 34*(1), 72–79. https://doi.org/10.1097/jcp.0000000000000051

Klinedinst, N. J., Dunbar, S. B., & Clark, P. C. (2012). Stroke survivor and informal caregiver perceptions of poststroke depressive symptoms. *Journal of Neuroscience Nursing, 44*(2), 72–81. https://doi.org/10.1097/jnn.0b013e3182477944

Knoflach, M., Matosevic, B., Rücker, M., Furtner, M., Mair, A., Wille, G., Zangerle, A., Werner, P., Ferrari, J., Schmidauer, C., Seyfang, L., Kiechl, S., Willeit, J., & Austrian Stroke Unit Registry Collaborators (2012). Functional recovery after ischemic stroke--a matter of age: Data from the Austrian Stroke Unit Registry. *Neurology, 78*(4), 279–285. https://doi.org/10.1212/WNL.0b013e31824367ab

Koenker, R., & Bassett, G. (1978). Regression quantiles. *Econometrica, 46*(1), 33. https://doi.org/10.2307/1913643

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9. *Journal of General Internal Medicine*, *16*(9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2003). The Patient Health Questionnaire-2: Validity of a Two-Item Depression Screener. *Medical Care, 41*, 1284-92.

Kruithof, W., Post, M., Leeuwen, C., Schepers, V., Bos, G., & Visser-Meily, J. (2015). Course of social support and relationships between social support and patients' depressive symptoms in the first 3 years post-stroke. *Journal of Rehabilitation Medicine, 47*(7), 599–604. https://doi.org/10.2340/16501977-1971

Kukull, W. A., & Ganguli, M. (2012). Generalizability: The trees, the forest, and the low-hanging fruit. *Neurology, 78*(23), 1886–1891. https://doi.org/10.1212/wnl.0b013e318258f812

Kutlubaev, M. A., & Hackett, M. L. (2014). Part II: Predictors of depression after stroke and impact of depression on stroke outcome: An updated systematic review of observational studies. *International Journal of Stroke, 9*(8), 1026–1036. https://doi.org/10.1111/ijs.12356

Kwah, L. K., & Diong, J. (2014). National Institutes of Health Stroke Scale (NIHSS). *Journal of Physiotherapy, 60*(1), 61. https://doi.org/10.1016/j.jphys.2013.12.012

Kwok, T., Lo, R. S., Wong, E., Wai-Kwong, T., Mok, V., & Kai-Sing, W. (2006). Quality of life of stroke survivors: A 1-year follow-up study. *Archives of Physical Medicine and Rehabilitation, 87*(9), 1177–1182. https://doi.org/10.1016/j.apmr.2006.05.015

Kwon, S., Hartzema, A. G., Duncan, P. W., & Lai, S. M. (2004). Disability Measures in Stroke: relationship among the Barthel Index, the Functional Independence Measure, and the modified Rankin Scale. *Stroke, 35*(4), 918–923. https://doi.org/10.1161/01.str.0000119385.56094.32

Ladwig, S., & Werheid, K. (2020). Determinants of antidepressant treatment and outpatient rehabilitation within the first year after stroke. Published. *Journal of Geriatric Psychiatry and Neurology.* https://doi.org/10.1177/0891988720973749

Lai, S. M., Duncan, P. W., Keighley, J., & Johnson, D. (2002a). Depressive symptoms and independence in BADL and IADL. *Journal of Rehabilitation Research and Development, 39*(5), 589–596. PMID: 17642023

Lai, S. M., Studenski, S., Duncan, P. W., & Perera, S. (2002b). Persisting consequences of stroke measured by the Stroke Impact Scale. *Stroke, 33*(7), 1840–1844. https://doi.org/10.1161/01.str.0000019289.15440.f2

Landreville, P., Desrosiers, J., Vincent, C., Verreault, R., & Boudreault, V. (2009). The role of activity restriction in poststroke depressive symptoms. *Rehabilitation Psychology, 54*(3), 315–322. https://doi.org/10.1037/a0016572

Lerdal, A., & Gay, C. L. (2013). Fatigue in the acute phase after first stroke predicts poorer physical health 18 months later. *Neurology, 81*(18), 1581–1587. https://doi.org/10.1212/wnl.0b013e3182a9f471

Levin, M. F., Kleim, J. A., & Wolf, S. L. (2009). What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabilitation and Neural Repair, 23*(4), 313–319. https://doi.org/10.1177/1545968308328727

Li, L. J., Yao, X. M., Guan, B. Y., Chen, Q., Zhang, N., & Wang, C. X. (2019). Persistent depression is a predictor of quality of life in stroke survivors: Results from a 5-year follow-up study of a Chinese cohort. *Chinese Medical Journal, 132*(18), 2206–2212. https://doi.org/10.1097/cm9.0000000000000400

Li, Q. X., Zhao, X. J., Wang, Y., Wang, D. L., Zhang, J., Liu, T. J., Peng, Y. B., Fan, H. Y., & Zheng, F. X. (2020). Value of the Barthel scale in prognostic prediction for patients with cerebral infarction. *BioMedical Central Cardiovascular Disorders, 20*(1). https://doi.org/10.1186/s12872-019-01306-1

Liang, Y., Chen, Y. K., Mok, V. C. T., Wang, D. F., Ungvari, G. S., Chu, W. C. W., Kang, H. J., & Tang, W. K. (2018). Cerebral small vessel disease burden is associated with poststroke depressive symptoms: A 15-month prospective study. *Frontiers in Aging Neuroscience, 10*(46). https://doi.org/10.3389/fnagi.2018.00046

Lim, G. Y., Tam, W. W., Lu, Y., Ho, C. S., Zhang, M. W., & Ho, R. C. (2018). Prevalence of depression in the community from 30 countries between 1994 and 2014. *Scientific Reports, 8(*1). https://doi.org/10.1038/s41598-018-21243-x

Lim, J. H., & Cheon, S. H. (2015). Analysis of variation in length of stay (LOS) after ischemic and hemorrhagic stroke using the Charlson Comorbidity Index (CCI). *Journal of Physical Therapy Science, 27*(3), 799–803. https://doi.org/10.1589/jpts.27.799

Lindén, T., Blomstrand, C., & Skoog, I. (2007). Depressive disorders after 20 months in elderly stroke patients. *Stroke*, 38(6), 1860–1863. https://doi.org/10.1161/strokeaha.106.471805

Lipowski, Z. J. (1985). The holistic approach to medicine. *Psychosomatic Medicine and Liaison Psychiatry*, 105–117. https://doi.org/10.1007/978-1-4613-2509-3_6

Liu, Z., Zhou, X., Zhang, W., & Zhou, L. (2020). Resilience is an independent correlate of the course of quality of life in patients with first-ever ischemic stroke. *International Psychogeriatrics*, 1–9. https://doi.org/10.1017/s1041610220000587

Lökk, J., & Delbari, A. (2010). Management of depression in elderly stroke patients. *Neuropsychiatric Disease and Treatment, 539*. https://doi.org/10.2147/ndt.s7637

Lopatkiewicz, A. M., Pera, J., Slowik, A., & Dziedzic, T. (2021). Association of early and later depressive symptoms with functional outcome after ischemic stroke. *Journal of Neural Transmission, 128*(5), 679–686. https://doi.org/10.1007/s00702-021-02328-w

Lundström, E., Isaksson, E., Greilert Norin, N., Näsman, P., Wester, P., Mårtensson, B., Norrving, B., Wallén, H., Borg, J., Hankey, G.J., Hackett, M.L., Mead, G.E., Dennis, M.S., & Sunnerhagen, K.S. (2021). Effects of Fluoxetine on Outcomes at 12 Months After Acute Stroke: Results From EFFECTS, a randomized controlled trial. *Stroke, 52*(10), 3082-3087. https://doi.org/10.1161/STROKEAHA.121.034705

Lynch, E. A., Mackintosh, S., Luker, J. A., & Hillier, S. L. (2019). Access to rehabilitation for patients with stroke in Australia. *Medical Journal of Australia, 210*(1), 21–26. https://doi.org/10.5694/mja2.12034

Ma, H., Parsons, M. W., Christensen, S., Campbell, B. C. V., Churilov, L., Connelly, A., Yan, B., Bladin, C., Phan, T., Barber, A. P., Read, S., Hankey, G. J., Markus, R., Wijeratne, T., Grimley, R., Mahant, N., Kleinig, T., Sturm, J., Lee, A., … Donnan, G. A. (2012). A Multicentre, randomized, double-blinded, placebo-controlled phase III study to investigate Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND). *International Journal of Stroke, 7*(1), 74–80. https://doi.org/10.1111/j.1747-4949.2011.00730.x

Mahoney, F. I., & Barthel, D. W. (1965). Functional evaluation: The Barthel index: A simple index of independence useful in scoring improvement in the rehabilitation of the chronically ill. *Maryland State Medical Journal, 14*, 61–65.

Majumdar, S., & Morris, R. (2018). Brief group-based acceptance and commitment therapy for stroke survivors. *British Journal of Clinical Psychology, 58*(1), 70–90. https://doi.org/10.1111/bjc.12198

Marks, I. M. (1986). *Behavioural Psychotherapy: Maudsley Pocket Book of Clinical Management,* Wright/IOP Publishing.

Matsuzaki, S., Hashimoto, M., Yuki, S., Koyama, A., Hirata, Y., & Ikeda, M. (2015). The relationship between post-stroke depression and physical recovery. *Journal of Affective Disorders, 176*, 56–60. https://doi.org/10.1016/j.jad.2015.01.020

Mayo, N. E., Wood-Dauphinee, S., Ahmed, S., Gordon, C., Higgins, J., McEwen, S., & Salbach, N. (1999). Disablement following stroke. *Disability and Rehabilitation, 21*(5-6), 258–268. https://doi.org/10.1080/096382899297684

Meader, N., Moe-Byrne, T., Llewellyn, A., & Mitchell, A. J. (2014). Screening for poststroke major depression: A meta-analysis of diagnostic validity studies. *Journal of Neurology, Neurosurgery and Psychiatry, 85*(2), 198–206. https://doi.org/10.1136/jnnp-2012-304194

Medeiros, G. C., Roy, D., Kontos, N., & Beach, S. R. (2020). Post-stroke depression: A 2020 updated review. *General Hospital Psychiatry, 66,* 70–80. https://doi.org/10.1016/j.genhosppsych.2020.06.011

Mitchell P. H. (2016). Nursing Assessment of Depression in Stroke Survivors. *Stroke, 47*(1), e1-e3. https://doi.org/10.1161/strokeaha.115.008362

Mitchell, A. J., Chan, M., Bhatti, H., Halton, M., Grassi, L., Johansen, C., & Meader, N. (2011). Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A meta-analysis of 94 interview-based studies. *The Lancet. Oncology, 12*(2), 160–174. https://doi.org/10.1016/S1470-2045(11)70002-x

Montgomery, S. A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry 134,* 382–389. https://doi.org/10.1192/bjp.134.4.382

Motulsky, H. (2018). *Intuitive biostatistics: A nonmathematical guide to statistical thinking* (4th ed.) Oxford University Press.

Morsund, S. H., Ellekjær, H., Gramstad, A., Reiestad, M. T., Midgard, R., Sando, S. B., Jonsbu, E., & Næss, H. (2019). The development of cognitive and emotional impairment after a minor stroke: A longitudinal study. Acta *Neurologica Scandinavica, 140*(4), 281–289. https://doi.org/10.1111/ane.13143

Mortensen, J. K., & Andersen, G. (2021). Pharmacological management of post-stroke depression: An update of the evidence and clinical guidance. *Expert Opinion on Pharmacotherapy, 22*(9), 1157–1166. https://doi.org/10.1080/14656566.2021.1880566

Mundt, J. C., Marks, I. M., Shear, M. K., & Greist, J. H. (2002). The Work and Social Adjustment Scale: A simple measure of impairment in functioning. *The British Journal of Psychiatry, 180*, 461–464. https://doi.org/10.1192/bjp.180.5.461

National Stroke Foundation (2021). *Clinical Guidelines for Stroke Management 2021*. https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management

National Stroke Foundation (2020). *National Stroke Audit – Rehabilitation Services Report 2020.* https://informme.org.au/stroke-data/Rehabilitation-audits

Nease, D. E., & Malouin, J. M. (2003). Depression screening: A practical strategy. *The Journal of Family Practice, 52*(2), 118-124. PMID: 12585989

Ohura, T., Hase, K., Nakajima, Y., & Nakayama, T. (2017). Validity and reliability of a performance evaluation tool based on the modified Barthel Index for stroke patients. *BioMedical Central Medical Research Methodology*, *17*(1). https://doi.org/10.1186/s12874-017-0409-2

Ormstad, H., Aass, H. C. D., Amthor, K. F., Lund-Sørensen, N., & Sandvik, L. (2012). Serum levels of cytokines, glucose, and hemoglobin as possible predictors of poststroke depression, and association with poststroke fatigue. *International Journal of Neuroscience, 122*(11), 682-690. https://doi.org/10.3109/00207454.2012.709892

Page, M. J., McKenzie, J. E., 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., . . . Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Systematic Reviews*, *10*(1). https://doi.org/10.1186/s13643-021-01626-4

Palstam, A., Sjödin, A., & Sunnerhagen, K. S. (2019). Participation and autonomy five years after stroke: A longitudinal observational study. *PLOS ONE, 14*(7), e0219513. https://doi.org/10.1371/journal.pone.0219513

Pancheri, P., & Carilli L. (1982). Standardizzazione e validazione di una nuova self rating-scale per la valutazione della sintomatologia depressiva. *Rivista di Psichiatria*, *17*, 32-37.

Paolucci, S., Iosa, M., Coiro, P., Venturiero, V., Savo, A., De Angelis, D., & Morone, G. (2019). Post-stroke depression increases disability more than 15% in ischemic stroke survivors: A case-control study. *Frontiers in Neurology, 10*(926). https://doi.org/10.3389/fneur.2019.00926

Paradiso, S., Ohkubo, T., & Robinson, R. G. (1997). Vegetative and psychological symptoms associated with depressed mood over the first two years after stroke. *The International Journal of Psychiatry in Medicine, 27*(2), 137–157. https://doi.org/10.2190/bwja-kqp3-7vuy-d06t

Pascoe, M. C., Crewther, S. G., Carey, L. M., & Crewther, D. P. (2011). Inflammation and depression: Why poststroke depression may be the norm and not the exception. *International Journal of Stroke 6*(2), 128–135. https://doi.org/10.1111/j.1747-4949.2010.00565.x

Patchick, E. L., Horne, M., Woodward-Nutt, K., Vail, A., & Bowen, A. (2015). Development of a patient-centred, patient-reported outcome measure (PROM) for post-stroke cognitive rehabilitation: Qualitative interviews with stroke survivors to inform design and content. *Health Expectations, 18*(6), 3213–3224. https://doi.org/10.1111/hex.12311

Perkins, A., Ridler, J., Browes, D., Peryer, G., Notley, C., & Hackmann, C. (2018). Experiencing mental health diagnosis: a systematic review of service user, clinician, and carer perspectives across clinical settings. *Lancet Psychiatry, 5*(9), 747-764. https://doi.org/10.1016/s2215-0366(18)30095-6

Phipps, M. S., & Cronin, C. A. (2020). Management of acute ischemic stroke. *British Medical Journal*, *368*, l6983. 1-15. https://doi.org/10.1136/bmj.l6983

Pohjasvaara, T., Vataja, R., Leppävuori, A., Kaste, M., & Erkinjuntti, T. (2001). Suicidal ideas in stroke patients 3 and 15 months after stroke. *Cerebrovascular Diseases, 12*(1), 21–26. https://doi.org/10.1159/000047676

Powers, W. J., Rabinstein, A. A., Ackerson, T., Adeoye, O. M., Bambakidis, N. C., Becker, K., Biller, J., Brown, M., Demaerschalk, B. M., Hoh, B., Jauch, E. C., Kidwell, C. S., Leslie-Mazwi, T. M., Ovbiagele, B., Scott, P. A., Sheth, K. N., Southerland, A. M., Summers, D. V., & Tirschwell, D. L. (2019). Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 50*(12). https://doi.org/10.1161/str.0000000000000211

Price-Haywood, E. G., Harden-Barrios, J., Carr, C., Reddy, L., Bazzano, L. A., & van Driel, M. L. (2018). Patient-reported outcomes in stroke clinical trials 2002–2016: A systematic review. *Quality of Life Research, 28*(5), 1119–1128. https://doi.org/10.1007/s11136-018-2053-7

Prisnie, J. C., Fiest, K. M., Coutts, S. B., Patten, S. B., Atta, C. A., Blaikie, L., Bulloch, A. G., Demchuk, A., Hill, M. D., Smith, E. E., & Jetté, N. (2016). Validating screening tools for depression in stroke and transient ischemic attack patients. *The International Journal of Psychiatry in Medicine, 51*(3), 262–277. https://doi.org/10.1177/0091217416652616

Quinn, T. J., Dawson, J., Walters, M. R., & Lees, K. R. (2009). Functional outcome measures in contemporary stroke trials. *International Journal of Stroke, 4*(3), 200–205. https://doi.org/10.1111/j.1747-4949.2009.00271.x

Quinn, T. J., Langhorne, P., & Stott, D. J. (2011). Barthel Index for stroke trials. *Stroke, 42*(4), 1146–1151. https://doi.org/10.1161/strokeaha.110.598540

Radloff, L.S. (1977). A CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385-401. https://doi.org/10.1177/014662167700100306

Rankin J. (1957) Cerebral vascular accidents in patients over the age of 60. *Scottish Medical Journal*, *2*(5)*,* 200-15. https://doi.org/10.1177/003693305700200401

Reeves, M., Lisabeth, L., Williams, L., Katzan, I., Kapral, M., Deutsch, A., & Prvu-Bettger, J. (2018). Patient-reported outcome measures (PROMs) for acute stroke: Rationale, methods and future directions. *Stroke, 49*(6), 1549–1556. https://doi.org/10.1161/strokeaha.117.018912

Rethnam, V., Bernhardt, J., Johns, H., Hayward, K. S., Collier, J. M., Ellery, F., Gao, L., Moodie, M., Dewey, H., Donnan, G. A., & Churilov, L. (2021). Look closer: The multidimensional patterns of post-stroke burden behind the modified Rankin Scale. *International Journal of Stroke, 16*(4), 420–428. https://doi.org/10.1177/1747493020951941

Richardson, M., Campbell, N., Allen, L., Meyer, M., & Teasell, R. (2015). The stroke impact scale: Performance as a quality of life measure in a community-based stroke rehabilitation setting. *Disability and Rehabilitation, 38*(14), 1425–1430. https://doi.org/10.3109/09638288.2015.1102337

Rimmele, D. L., Lebherz, L., Frese, M., Appelbohm, H., Bartz, H. J., Kriston, L., Gerloff, C., Härter, M., & Thomalla, G. (2019). Outcome evaluation by patient reported outcome measures in stroke clinical practice (EPOS) protocol for a prospective observation and implementation study. *Neurological Research and Practice, 1*(28). https://doi.org/10.1186/s42466-019-0034-0

Robinson-Smith, G., Johnston, M. V., & Allen, J. (2000). Self-care self-efficacy, quality of life, and depression after stroke. *Archives of Physical Medicine and Rehabilitation, 81*(4), 460–464.https://doi.org/10.1053/mr.2000.3863

Robinson, R. G., & Jorge, R. E. (2016). Post-stroke depression: A review. *American Journal of Psychiatry, 173*(3), 221–231. https://doi.org/10.1176/appi.ajp.2015.15030363

Rogers, S. C. (2017). Poststroke depression screening: An executive summary. *Journal of Neuroscience Nursing, 49*(2), 66–68. https://doi.org/10.1097/jnn.0000000000000270

Rost, N. S., Bottle, A., Lee, J., Randall, M., Middleton, S., Shaw, L., Thijs, V., Rinkel, G. J. E., & Hemmen, T. M. (2016). Stroke severity is a crucial predictor of outcome: An international prospective validation study. *Journal of the American Heart Association, 5*(1), e002433. https://doi.org/10.1161/jaha.115.002433

Roth, M. (1955). The natural history of mental disorder in old age. *Journal of Mental Science, 101*(423), 281-301. doi:10.1192/bjp.101.423.281

The Royal Australian College of General Practitioners. (2016). *Guidelines for preventive activities in general practice* (9th ed). RACGP. https://www.racgp.org.au/running-a-practice/practice-resources/ordering-publications/guidelines-for-general-practice

Royal College of Physicians. (2016, October) *National clinical guideline for stroke (5th ed.)*. https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines

Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J. J., 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., … Council on Nutrition, Physical Activity and Metabolism (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

Sagen, U., Vik, T. G., Moum, T., Mørland, T., Finset, A., & Dammen, T. (2009). Screening for anxiety and depression after stroke: Comparison of the Hospital Anxiety and Depression Scale and the Montgomery and Åsberg Depression Rating Scale. *Journal of Psychosomatic Research, 67*(4), 325–332. https://doi.org/10.1016/j.jpsychores.2009.03.007

Salter, K., Hellings, C., Foley, N., & Teasell, R. (2008). The experience of living with stroke: A qualitative meta-synthesis. *Journal of Rehabilitation Medicine, 40*(8), 595–602. https://doi.org/10.2340/16501977-0238

Sangam, S. (2018). Post-stroke depression: Epidemiology, diagnosis, risk factors, and management. *Journal of Neurological Disorders, 6*(394). https://doi.org/10.4172/23296895-1000394

Sangha, H., Lipson, D., Foley, N., Salter, K., Bhogal, S., Pohani, G., & Teasell, R. W. (2005). A comparison of the Barthel Index and the Functional Independence Measure as outcome measures in stroke rehabilitation: Patterns of disability scale usage in clinical trials. *International Journal of Rehabilitation Research, 28*(2), 135–139. https://doi.org/10.1097/00004356-200506000-00006

Schepers, V., Post, M., Visser-Meily, A., van de Port, I., Akhmouch, M., & Lindeman, E. (2009). Prediction of depressive symptoms up to three years post-stroke. *Journal of Rehabilitation Medicine, 41*(11), 930–935. https://doi.org/10.2340/16501977-0446

Schindel, D., Schneider, A., Grittner, U., Jöbges, M., & Schenk, L. (2019). Quality of life after stroke rehabilitation discharge: A 12-month longitudinal study. *Disability and Rehabilitation, 43*(16), 2332-2341. https://doi.org/10.1080/09638288.2019.1699173

Schlegel, D., Kolb, S. J., Luciano, J. M., Tovar, J. M., Cucchiara, B. L., Liebeskind, D. S., & Kasner, S. E. (2003). Utility of the NIH Stroke Scale as a predictor of hospital disposition. *Stroke, 34*(1), 134–137. https://doi.org/10.1161/01.str.0000048217.44714.02

Schöttke, H., Gerke, L., Düsing, R., & Möllmann, A. (2020). Post-stroke depression and functional impairments – A 3-year prospective study. *Comprehensive Psychiatry*, *10*, 152171. https://doi.org/10.1016/j.comppsych.2020.152171

Schultz, S. K., Castillo, C. S., Rosier, J. T., & Robinson, R. G. (1997). Generalized anxiety and depression: Assessment over 2 years after stroke. *The American Journal of Geriatric Psychiatry, 5*(3), 229–237. https://doi.org/10.1097/00019442-199700530-00007

Shankar, L., Smith, N., Uchino, K., Thompson, N. R., Pozuelo, L., & Katzan, I. L. (2017). Evaluation of the Patient Health Questionnaire-2 as a screening tool for depression during the acute stroke admission. *Journal of Stroke and Cerebrovascular Diseases, 26*(11), 2519–2526. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.05.044

Shapiro, P. A. (2015). Management of depression after myocardial infarction. *Current Cardiology Reports, 17*(10). https://doi.org/10.1007/s11886-015-0634-4

Shi, Y. Z., Xiang, Y. T., Wu, S. L., Zhang, N., Zhou, J., Bai, Y., Wang, S., Wang, Y. L., Zhao, X. Q., Ungvari, G. S., Chiu, H. F. K., Wang, Y. J., & Wang, C. X. (2014). The relationship between frontal lobe lesions, course of post-stroke depression, and 1-year prognosis in patients with first-ever ischemic stroke. *PLoS ONE, 9*(7), e100456. https://doi.org/10.1371/journal.pone.0100456

Shi, Y., Xiang, Y., Yang, Y., Zhang, N., Wang, S., Ungvari, G. S., Chiu, H. F., Tang, W. K., Wang, Y., Zhao, X., Wang, Y., & Wang, C. (2015). Depression after minor stroke: Prevalence and predictors. *Journal of Psychosomatic Research, 79*(2), 143–147. https://doi.org/10.1016/j.jpsychores.2015.03.012

Sibon, I., Lassalle-Lagadec, S., Renou, P., & Swendsen, J. (2012). Evolution of depression symptoms following stroke: A prospective study using computerized ambulatory monitoring. *Cerebrovascular Diseases, 33*(3), 280–285. https://doi.org/10.1159/000334663

Sit, J. W. H., Wong, T. K. S., Clinton, M., & Li, L. S. W. (2007). Associated factors of post stroke depression among Hong Kong Chinese: A longitudinal study. *Psychology, Health and Medicine, 12*(2), 117–125. https://doi.org/10.1080/14622200500358978

Skoglund, E., Westerlind, E., Persson, H., & Sunnerhagen, K. (2019). Self-perceived impact of stroke: A longitudinal comparison between one and five years post-stroke. *Journal of Rehabilitation Medicine, 51*(9), 660–664. https://doi.org/10.2340/16501977-2595

Snaith, R. P., Harrop, F. M., Newby, D. A., & Teale, C. (1986). Grade scores of the Montgomery—Åsberg depression and the clinical anxiety scales. *British Journal of Psychiatry, 148*(5), 599–601. https://doi.org/10.1192/bjp.148.5.599

Snögren, M., & Sunnerhagen, K. S. (2009). Description of functional disability among younger stroke patients: Exploration of activity and participation and environmental factors. *International Journal of Rehabilitation Research, 32*(2), 124–131. https://doi.org/10.1097/mrr.0b013e328325a5be

Sperandei, S. (2014). Understanding logistic regression analysis. *Biochemia Medica, 24*(1), 12–18. https://doi.org/10.11613/bm.2014.003

Spitzer, R. L., Williams, J. B. W., Kroenke, K., Linzer, M., DeGruy F. V., Hahn, S. R., Brody, D. & Johnson, J. G. (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *The Journal of the American Medical Association, 272*(22), 1749–1756. https://doi.org/10.1001/jama.272.22.1749

Staples, L. G., Dear, B. F., Gandy, M., Fogliati, V., Fogliati, R., Karin, E., Nielssen, O., & Titov, N. (2019). Psychometric properties and clinical utility of brief measures of depression, anxiety, and general distress: The PHQ-2, GAD-2, and K-6. *General Hospital Psychiatry, 56*, 13-18. https://doi.org/10.1016/j.genhosppsych.2018.11.003

Starkstein, S. E., & Hayhow, B. D. (2019). Treatment of post-stroke depression. *Current Treatment Options in Neurology, 21*(7). https://doi.org/10.1007/s11940-019-0570-5

StataCorp. (2015). Stata Statistical Software: Release 14 College Station, TX: StataCorp LLC [Computer software]. https://www.stata.com/

StataCorp. (2019). Stata Statistical Software: Release 16 College Station, TX: StataCorp LLC. [Computer software]. https://www.stata.com/

Stewart, J. C., & Cramer, S. C. (2013). Patient-reported measures provide unique insights into motor function after stroke. *Stroke, 44*(4), 1111–1116. https://doi.org/10.1161/strokeaha.111.674671

Sugawara, N., Metoki, N., Hagii, J., Saito, S., Shiroto, H., Tomita, T., Yasujima, M., Okumura, K., & Yasui-Furukori, N. (2015). Effect of depressive symptoms on the length of hospital stay among patients hospitalized for acute stroke in Japan. *Neuropsychiatric Disease and Treatment*, 2551-2556. https://doi.org/10.2147/ndt.s91303

Swartz, R. H., Bayley, M., Lanctôt, K. L., Murray, B. J., Cayley, M. L., Lien, K., Sicard, M. N., Thorpe, K. E., Dowlatshahi, D., Mandzia, J. L., Casaubon, L. K., Saposnik, G., Perez, Y., Sahlas, D. J., & Herrmann, N. (2016). Post-stroke depression, obstructive sleep apnea, and cognitive impairment: Rationale for, and barriers to, routine screening. *International Journal of Stroke, 11*(5), 509–518. https://doi.org/10.1177/1747493016641968

Tellier, M., & Rochette, A. (2009). Falling through the cracks: A literature review to understand the reality of mild stroke survivors. *Topics in Stroke Rehabilitation, 16*(6), 454-462. https://doi.org/10.1310/tsr1606-454

Teoh, V., Sims, J., & Milgrom, J. (2009). Psychosocial predictors of quality of life in a sample of community-dwelling stroke survivors: A longitudinal study. *Topics in Stroke Rehabilitation, 16*(2), 157–166. https://doi.org/10.1310/tsr1602-157

Terrill, A. L., Schwartz, J. K., & Belagaje, S. R. (2018). Best practices for the interdisciplinary rehabilitation team: A review of mental health issues in mild stroke survivors. *Stroke Research and Treatment,* 1-8. https://doi.org/10.1155/2018/6187328

Tessier, A., Finch, L., Daskalopoulou, S. S., & Mayo, N. E. (2008). Validation of the Charlson comorbidity index for predicting functional of stroke. *Archives of Physical Medicine and Rehabilitation, 89*(7), 1276–1283. https://doi.org/10.1016/j.apmr.2007.11.049

Thandi, G., Fear, N. T., & Chalder, T. (2017). A comparison of the Work and Social Adjustment Scale (WSAS) across different patient populations using Rasch analysis and exploratory factor analysis. *Journal of Psychosomatic Research, 92*, 45–48. https://doi.org/10.1016/j.jpsychores.2016.11.009

Thayabaranathan, T., Andrew, N. E., Kilkenny, M. F., Stolwyk, R., Thrift, A. G., Grimley, R., Johnston, T., Sundararajan, V., Lannin, N. A., & Cadilhac, D. A. (2018). Factors influencing self reported anxiety or depression following stroke or TIA using linked registry and hospital data. *Quality of Life Research, 27*(12), 3145–3155. https://doi.org/10.1007/s11136-018-1960-y

Thombs, B. D., Bass, E. B., Ford, D. E., Stewart, K. J., Tsilidis, K. K., Patel, U., Fauerbach, J. A., Bush, D. E., & Ziegelstein, R. C. (2006). Prevalence of depression in survivors of acute myocardial infarction. *Journal of General Internal Medicine, 21*(1), 30–38. https://doi.org/10.1111/j.1525-1497.2005.00269.x

Tiedman, C., Suthers, B., Julien, B., Hackett, A., & Oakley, P. (2019). Management of stroke in the Australian Indigenous population: from hospitals to communities. *International Medical Journal, 49*(8), 962-968. https://doi.org/10.1111/imj.14303

Towfighi, A., Ovbiagele, B., El Husseini, N., Hackett, M. L., Jorge, R. E., Kissela, B. M., Mitchell, P. H., Skolarus, L. E., Whooley, M. A., Williams, L. S., & American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research (2017). Poststroke depression: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 48*(2), e30–e43. https://doi.org/10.1161/STR.0000000000000113

Townend, B., Whyte, S., Desborough, T., Crimmins, D., Markus, R., Levi, C., & Sturm, J. (2007). Longitudinal prevalence and determinants of early mood disorder post-stroke. *Journal of Clinical Neuroscience, 14*(5), 429–434. https://doi.org/10.1016/j.jocn.2006.01.025

Tse, T., Binte Yusoff, S. Z., Churilov, L., Ma, H., Davis, S., Donnan, G. A., & Carey, L. M. (2017b). Increased work and social engagement is associated with increased stroke specific quality of life in stroke survivors at 3 months and 12 months post-stroke: A longitudinal study of an Australian stroke cohort. *Topics in Stroke Rehabilitation, 24*(6), 405–414. https://doi.org/10.1080/10749357.2017.1318339

Tse, T., Douglas, J., Lentin, P., Lindén, T., Churilov, L., Ma, H., Davis, S., Donnan, G., & Carey, L. (2017a). Reduction in retained activity participation is associated with depressive symptoms 3 months after mild stroke: An observational cohort study. *Journal of Rehabilitation Medicine, 49*(2), 120–127. https://doi.org/10.2340/16501977-2184

Tse, T., Linden, T., Churilov, L., Davis, S., Donnan, G., & Carey, L. M. (2019). Longitudinal changes in activity participation in the first year post-stroke and association with depressive symptoms. *Disability and Rehabilitation, 41*(21), 2548–2555. https://doi.org/10.1080/09638288.2018.1471742

Turhan, N., Atalay, A., & Muderrisoglu, H. (2009). Predictors of functional outcome in first-ever ischemic stroke: A special interest to ischemic subtypes, comorbidity and age. *NeuroRehabilitation, 24*(4), 321–326. https://doi.org/10.3233/nre-2009-0485

Twisk, J., & de Vente, W. (2002). Attrition in longitudinal studies. *Journal of Clinical Epidemiology, 55*(4), 329–337. https://doi.org/10.1016/s0895-4356(01)00476-0

Uyttenboogaart, M., Luijckx, G. J., Vroomen, P. C. A. J., Stewart, R. E., & Keyser, J. (2007). Measuring disability in stroke: Relationship between the modified Rankin scale and the Barthel index. *Journal of Neurology, 254*(8), 1113–1117. https://doi.org/10.1007/s00415-007-0646-0

Veritas Health Innovation (2021). Covidence: Covidence Systematic Review Software. [Web based software]. https://www.covidence.org/

van der Kemp, J., Kruithof, W. J., Nijboer, T. C. W., van Bennekom, C. A. M., van Heugten, C., & Visser-Meily, J. M. A. (2017). Return to work after mild-to-moderate stroke: Work satisfaction and predictive factors. *Neuropsychological Rehabilitation, 29*(4), 638–653. https://doi.org/10.1080/09602011.2017.1313746

van Rijsbergen, M. W., Mark, R. E., Kop, W. J., de Kort, P. L., & Sitskoorn, M. M. (2020). Course and predictors of subjective cognitive complaints during the first 12 months after stroke. *Journal of Stroke and Cerebrovascular Diseases, 29*(3), 104588. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104588

Vanhook, P. (2009). The domains of stroke recovery. *Journal of Neuroscience Nursing, 41*(1), 6–17. https://doi.org/10.1097/jnn.0b013e31819345e4

Verdelho, A., Henon, H., Lebert, F., Pasquier, F., & Leys, D. (2004). Depressive symptoms after stroke and relationship with dementia: A three-year follow-up study. *Neurology, 62*(6), 905–911. https://doi.org/10.1212/01.wnl.0000115107.66957.8c

Volz, M., Ladwig, S., & Werheid, K. (2019). Gender differences in post-stroke depression: A longitudinal analysis of prevalence, persistence and predictive value of known risk factors. *Neuropsychological Rehabilitation, 31*(1), 1–17. https://doi.org/10.1080/09602011.2019.1648301

Vyas, M. V., Hackam, D. G., Silver, F. L., Laporte, A., & Kapral, M, K. (2016) Lost productivity in stroke survivors: An econometrics analysis. *Neuroepidemiology, 47*, 164–170. doi: 10.1159/000454730

Vyas, M. V., Wang, J. Z., Gao, M. M., & Hackam, D. G. (2021). Association between stroke and subsequent risk of suicide. *Stroke, 52*(4), 1460–1464. https://doi.org/10.1161/strokeaha.120.032692

Wallace, D., Duncan, P. W., & Lai, S. M. (2002). Comparison of the responsiveness of the Barthel Index and the Motor Component of the Functional Independence Measure in stroke. *Journal of Clinical Epidemiology, 55*(9), 922–928. https://doi.org/10.1016/s0895-4356(02)00410-9

Wang, S. B., Wang, Y. Y., Zhang, Q. E., Wu, S. L., Ng, C. H., Ungvari, G. S., Chen, L., Wang, C. X., Jia, F. J., & Xiang, Y. T. (2018). Cognitive behavioral therapy for post-stroke depression: A meta-analysis. *Journal of Affective Disorders, 235*, 589–596. https://doi.org/10.1016/j.jad.2018.04.011

Wardlaw, J. M., Murray, V., Berge, E., & del Zoppo, G. J. (2014). Thrombolysis for acute ischaemic stroke. *The Cochrane Database of Systematic Reviews, 7*. 1-141. https://doi.org/10.1002/14651858.CD000213.pub3

White, C. L., McClure, L. A., Wallace, P. M., Braimah, J., Liskay, A., Roldan, A., & Benavente, O. R. (2011). The correlates and course of depression in patients with lacunar stroke: Results from the secondary prevention of small subcortical strokes (SPS3) study. *Cerebrovascular Diseases, 32*(4), 354–360. https://doi.org/10.1159/000330350

White, J. H., Attia, J., Sturm, J., Carter, G., & Magin, P. (2014). Predictors of depression and anxiety in community dwelling stroke survivors: A cohort study. *Disability and Rehabilitation, 36*(23), 1975–1982. https://doi.org/10.3109/09638288.2014.884172

White, J. H., Magin, P., Attia, J., Sturm, J., Carter, G., & Pollack, M. (2012). Trajectories of psychological distress after stroke. *The Annals of Family Medicine, 10*(5), 435–442. https://doi.org/10.1370/afm.1374

Williams, J. B. W., & Kobak, K. A. (2008). Development and reliability of a Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA). *British Journal of Psychiatry, 192*(1), 52–58. https://doi.org/10.1192/bjp.bp.106.032532

Wilson, J. M. G., & Jungner, G. (1968). Principles and Practice of Screening for Disease. *Annals of Internal Medicine, 69*(5), 1085. https://doi.org/10.7326/0003-4819-69-5-1085_2

Wilz, G., & Barskova, T. (2007). Predictors of psychological and somatic components of poststroke depression: A longitudinal study. *Topics in Stroke Rehabilitation, 14*(3), 25–40. https://doi.org/10.1310/tsr1403-25

Wolf, T. J., Baum, C., & Connor, L. T. (2009). Changing face of stroke: Implications for occupational therapy practice. *American Journal of Occupational Therapy, 63*(5), 621–625. https://doi.org/10.5014/ajot.63.5.621

Wolters, F. J., Li, L., Gutnikov, S. A., Mehta, Z., & Rothwell, P. M. (2018). Medical attention seeking after transient ischemic attack and minor stroke before and after the UK Face, Arm, Speech, Time (FAST) public education campaign. *JAMA Neurology*, *75*(10), 1225. https://doi.org/10.1001/jamaneurol.2018.1603

World Health Organisation. (1971). *Cerebrovascular Disease: Prevention, Treatment, and Rehabilitation*. World Health Organisation Technical Report Series, no. 469: Report of a WHO meeting. World Health Organisation, Geneva.

World Health Organisation. (2020). *Screening Programmes: A Short Guide. Increase Effectiveness, Maximize Benefits and Minimize harm*. Copenhagen: WHO Regional Office for Europe. ISBN: 9789289054782. https://www.euro.who.int/en/publications/abstracts/screening-programmes-a-short-guide.-increase-effectiveness,-maximize-benefits-and-minimize-harm-2020

Wu, Q. E., Zhou, A. M., Han, Y. P., Liu, Y. M., Yang, Y., Wang, X. M., & Shi, X. (2019). Poststroke depression and risk of recurrent stroke: A meta-analysis of prospective studies. *Medicine, 98*(42), e17235. https://doi.org/10.1097/MD.0000000000017235

Yesavage, J. A., Brink, T., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, *17*(1), 37–49. https://doi.org/10.1016/0022-3956(82)90033-4

Yiu, J., Miller, W. C., Eng, J. J., & Liu, Y. (2012). Longitudinal analysis of balance confidence in individuals with stroke using a multilevel model for change. *Neurorehabilitation and Neural Repair, 26*(8), 999–1006. https://doi.org/10.1177/1545968312437941

Young, F. B., Weir, C. J., & Lees, K. R. (2005). Comparison of the National Institutes of Health Stroke Scale with disability outcome measures in acute stroke trials. *Stroke, 36*(10), 2187-2192. https://doi.org/10.1161/01.str.0000181089.41324.70

Ytterberg, C., Dybäck, M., Bergström, A., Guidetti, S., & Eriksson, G. (2017). Perceived impact of stroke six years after onset, and changes in impact between one and six years. *Journal of Rehabilitation Medicine, 49*(8), 637–643. https://doi.org/10.2340/16501977-2258

Zhao, H., Campbell, B. C. V., Foster, S., Stephenson, M., Coote, S., Langenberg, F., Easton, D., Donnan, G. A., & Davis, S. M..(2021). Advances in pre-hospital care - operational experiences from the Melbourne mobile stroke unit. *Vessel Plus,* 5(10). https://doi.org/10.20517/2574 1209.2020.77

Zhou, X., Liu, Z., Zhang, W., & Zhou, L. (2020). Resilience is associated with post-stoke depression in Chinese stroke survivors: A longitudinal study. *Journal of Affective Disorders, 273*, 402–409. https://doi.org/10.1016/j.jad.2020.04.042

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica, 67(*6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Zulim, P., Perera, A., Stutzman, S., & Olson, D. (2019). Psychiatric nurses providing post-stroke depression education to care partners of stroke: A pilot study. *Journal of Health and Caring Sciences, 1*(2), 73–81. https://doi.org/10.37719/jhcs.2019.v1i2.oa005

Zung, W. W. K. (1965). A Self-Rating Depression Scale. *Archives of General Psychiatry*, *12*(1), 63. https://doi.org/10.1001/archpsyc.1965.01720310065008

Appendices

Appendix A

Database Syntax

Medline syntax: **exp Depression/** OR depress* OR depress* symptom* mp. OR post stroke depress* mp. OR PSD.mp. AND **exp Brain Ischemia/** OR **exp Cerebral Hemorrhage/** OR **exp Cerebral Infarction/** OR **exp Cerebrovascular Disorders/** OR **exp Stroke/** OR brain infarct* mp. OR brain isch*mia mp. OR cerebral h*morrhage mp. OR cerebral infarct*.mp. OR cerebral isch*mia mp. OR cerebral stroke.mp. OR cerebrovascular accident mp. OR cerebrovascular disease.mp. OR cerebrovascular disorder.mp. OR cerebrovascular stroke.mp. OR CVA mp. OR h*morrhagic stroke.mp. OR isch*mic stroke.mp. OR stroke.mp. AND **exp Longitudinal Studies/** OR course*.mp. OR longitudinal.mp. OR longitudinal stud*.mp. OR over time.mp. OR trajector*.mp.

PsycINFO syntax: **exp "Depression (Emotion)"/** OR depress* OR depress* symptom* mp. OR post stroke depress* mp. OR PSD mp. AND **exp Cerebral Hemorrhage/** OR **exp Cerebral Ischemia/** OR **exp Cerebrovascular Accidents/** OR **exp Cerebrovascular Disorders/** OR brain infarct*.mp. OR brain isch*mia mp. OR cerebral h*morrhage mp. OR cerebral infarct* mp. OR cerebral isch*mia.mp. OR cerebral stroke mp. OR cerebrovascular accident mp. OR cerebrovascular disease mp. OR cerebrovascular disorder mp. OR cerebrovascular stroke.mp. OR CVA.mp. OR h*morrhagic stroke mp. OR isch*mic stroke.mp. OR stroke.mp. AND **exp Longitudinal Studies/** OR course*.mp. OR longitudinal.mp. OR longitudinal stud*.mp. OR over time mp. OR trajector* mp.

Embase syntax: **exp depression/** OR **exp post-stroke depression/** OR depress*.mp. OR depress* symptom*.mp. OR post stroke depress*.mp. OR PSD.mp. AND **exp brain ischemia/** OR **exp cerebrovascular accident/** OR **exp cerebrovascular disease/** OR brain infarct*.mp. OR brain isch*mia mp. OR cerebral h*morrhage mp. OR cerebral infarct* mp. OR cerebral isch*mia.mp. OR cerebral stroke mp. OR cerebrovascular accident mp. OR cerebrovascular disease.mp. OR cerebrovascular disorder mp. OR cerebrovascular stroke.mp. OR CVA.mp. OR h*morrhagic stroke mp. OR isch*mic stroke.mp. OR stroke.mp. AND **exp longitudinal study/** OR course* mp. OR longitudinal mp. OR longitudinal stud*.mp. OR over time mp. OR trajector* mp.

CINAHL syntax: **MH Depression+** OR depress* OR "depress* symptom*" OR "post stroke depression" OR "post stroke depression" or psd AND **MH Cerebral Ischemia +** OR **MH Cerebrovascular Disorders +** OR **MH Stroke +** OR "brain infarct*" OR "brain isch*mia" OR "cerebral h*morrhage" OR "cerebral infarct*" OR "cerebral isch*mia" OR "cerebral stroke" OR "cerebrovascular accident" OR "cerebrovascular disease" OR "cerebrovascular disorder" OR "cerebrovascular stroke" OR CVA OR "h*morrhagic stroke" OR "isch*mic stroke" OR stroke AND course OR longitudinal OR "longitudinal stud*" OR "over time" OR trajector*

Note. Subject headings are listed in boldface.

Appendix B

Data Extracted in Review of Longitudinal Cohort Studies

Study details
Study (first author's surname, year published)
Author (first author's surname)
Title
Country in which the study was conducted
Larger cohort (i.e., if the cohort of stroke survivors was part of a larger cohort or program)
Study duration
Number of time points
Demographic and clinical characteristics
Number of participants at baseline
Stroke type (categorised as either 'ischemic', 'mixed', or 'not reported')
Number and percentage of ischaemic stroke participants at baseline
Number and percentage of haemorrhagic stroke participants at baseline
Number and percentage of other stroke types at baseline
First stroke cohort (categorised as either 'yes' or 'no')
Number of first strokes (i.e., number of participants without a history of stroke prior to the index stroke)
Mean age of the cohort at baseline (and corresponding standard deviation)
Number and percentage of females
Number and percentage of participants with a pre-stroke history of depression, if reported
Assessment of pre-stroke history of depression, if reported
Mean NIHSS score of the cohort at baseline (and corresponding standard deviation), if reported
Mean mRS score of the cohort at baseline (and corresponding standard deviation), if reported

Appendix C

Formulae for Extracting Study Results and Converting to the Desired Format

Formula 1:

Formula for calculating standard deviation (SD) from standard error (SE)

$$SD = SE \times \sqrt{N}$$

Note. N = sample size

Formula 2:

Formula for calculating standard deviation (SD) from 95% confidence interval

$$SD = [(UL - LL) / 3.92)] \times \sqrt{N}$$

Note. UL = 95% CI upper limit; LL = 95% CI lower limit; *N* = sample size
The value 3.92 is derived from the z-value of the 95% CI (1.96) multiplied by 2.

Formula 3:

Formula for calculating 95% CI from frequency and sample size

$$95\%\ CI = p \pm z * \sqrt{[p(1-p)/n]}$$

Note. p = frequency (0 to 1); z = 1.959964 (z-value for 0.95 probability); *n* = sample size

Cochrane Collaboration (2011, March). *Cochrane Handbook for Systematic Reviews of Interventions. 7.7 Extracting study results and converting to the desired format.* https://handbook-5-1.cochrane.org/chapter_7/7_7_extracting_study_results_and_converting_to_the_desired.htm

Appendix D

Detailed eligibility criteria for participation in START PrePARE and EXTEND

START PrePARE and START EXTEND	
Inclusion criteria: • Clinically confirmed ischaemic stroke • Patient was 18 years or older	Exclusion criteria: • Patients who were non-English speaking • Significant premorbid disability as determined by a mRS score ≥ 3 or more • A terminal illness in which the patient would not be expected to survive more than one year • Intracranial haemorrhage (IHC) identified by advanced clinical imaging MRI or CT
START EXTEND	
Inclusion criteria: • Treatment could have commenced after 3 hours and up to and including 9 hours following the stroke onset according to registered product information, or treatment could have commenced more than 4.5 hours and up to and including 9 hours post-stroke – according to locally accepted guidelines. • Patients who wake with stroke may have been included – if neurological-related and other relevant criteria had been satisfied. A 'wake-up' stroke is defined as the experience in which no symptoms of stroke are observed prior to sleep, however symptoms are experienced upon waking. For wake-up strokes, the midpoint between sleep onset and time of waking is recorded as the time of stroke onset. In these instances, the maximum period of time for randomisation is 9 hours from the recorded midpoint time (in lieu of the time of stroke onset). • An NIHSS score ≥ 4 to 26 with clinical signs of hemispheric infarction.	Exclusion criteria: • Rapidly improving symptoms, particularly if in the judgement of the managing clinician the improvement I s likely to result in the patient having an NIHSS score of < 4 at randomisation • Contraindication to the use of imaging contrast agents • Infarct core > 1/3 middle cerebral artery (MCA) territory qualitatively on CT • Participation in any study in the previous 30 days • Any condition that could impose hazards to the patient or effect participation in the study (this applies to patients with severe microangiopathy such as haemolytic uremic syndrome or thrombotic thrombocytopenic purpura) at the discretion of the investigator • Stroke within the last three-months; recent history or clinical presentation of ICH, sub-arachnoid haemorrhage, arteriovenous malformation, aneurysm, or cerebral neoplasm - at the discretion of the investigator • Current use of oral anticoagulants and a prolonged prothrombin time (international normalised ration > 1.6) • Use of heparin, expect for low-dose sub-cutaneous heparin, in the previous 48 hours and a prolonged activated partial thromboplastin time exceeding the upper limit of the local laboratory normal range • Use of glycoprotein IIb-IIIa inhibitors (clopidogrel and/or low-dose aspirin) prior to study entry is permitted • Clinically significant hypoglycaemia • Uncontrolled hypertension defined by a blood pressure > 185 mm Hg systolic or >110 mm Hg diastolic on at least two separate occasions at least 10 minutes apart, or requiring aggressive treatment to reduce the blood pressure to within these limits, at the discretion of the investigator • Hereditary or acquired haemorrhagic diathesis • Gastrointestinal or urinary bleeding within the preceding 21 days • Major surgery within the preceding 14 days which poses risk in the opinion of the investigator • Exposure to a thrombolytic agent within the previous 72 hours
START EXTEND RCT Specific imaging inclusion criteria:	
Penumbral mismatch – a penumbra to core' lesion volume ratio of greater than 1-2 and an absolute difference greater than 10 ml (using a MR or CT T_{max} > 6-s delay perfusion lesion and MR-DWI or CT-CBF core lesion) and an infarct core lesion volume less than or equal to 70ml using MR-DWI or CT-CBF	

Appendix E

Ethics Approval

Central ethical approval for this study was obtained from Melbourne Health Human Research Ethics Committee (2009.079) and Austin Health Human Research Ethics Committee (H2010/03588). Approval was also obtained from each recruiting hospital site and linked universities.

LA TROBE UNIVERSITY

RESEARCH SERVICES

MEMORANDUM

To:	**Professor Leeanne Carey, School of OT, Faculty of Health Sciences** **Ms. Tamara Tse, School of OT, Faculty of Health Sciences**
From:	**Secretary, La Trobe University Human Ethics Committee**
Subject:	**Review of Human Ethics Committee Application No. 10-071**
Title:	**Prediction and Prevention to Achieve Optimal Recovery Endpoints after stroke (PrePARE)**
Date:	**19 September 2010**

Thank you for your recent correspondence in relation to the research project referred to above. The project has been assessed as complying with the *National Statement on Ethical Conduct in Human Research*. I am pleased to advise that your project has been granted ethics approval and you may commence the study.

The project has been approved from the date of this letter until 31 December 2013.

Please note that your application has been reviewed by a sub-committee of the University Human Ethics Committee (UHEC) to facilitate a decision about the study before the next Committee meeting. This decision will require ratification by the full UHEC at its next meeting and the UHEC reserves the right to alter conditions of approval or withdraw approval. You will be notified if the approval status of your project changes.

The following standard conditions apply to your project:

- **Limit of Approval.** Approval is limited strictly to the research proposal as submitted in your application while taking into account any additional conditions advised by the UHEC.
- **Variation to Project.** Any subsequent variations or modifications you wish to make to your project must be formally notified to the UHEC for approval in advance of these modifications being introduced into the project. This can be done using the appropriate form: *Ethics - Application for Modification to Project* which is available on the Research Services website at *http://www.latrobe.edu.au/research-services/ethics/human.htm*. If the UHEC considers that the proposed changes are significant, you may be required to submit a new application form for approval of the revised project.
- **Adverse Events.** If any unforeseen or adverse events occur, including adverse effects on participants, during the course of the project which may affect the ethical acceptability of the project, the Chief Investigator must immediately notify the UHEC Secretary on telephone (03) 9479 1443. Any complaints about the project received by the researchers must also be referred immediately to the UHEC Secretary.

- **Withdrawal of Project.** If you decide to discontinue your research before its planned completion, you must advise the UHEC and clarify the circumstances.

- **Annual Progress Reports.** If your project continues for more than 12 months, you are required to submit an *Ethics - Progress/Final Report Form* annually, **on or just prior to 12 February**. The form is available on the Research Services website (see above address). Failure to submit a Progress Report will mean approval for this project will lapse. An audit may be conducted by the UHEC at any time.

- **Final Report.** A Final Report (see above address) is required within six months of the completion of the project or by **30 June 2014.**

If you have any queries on the information above or require further clarification please contact me through Research Services on telephone (03) 9479-1443, or e-mail at:

humanethics@latrobe.edu.au.

On behalf of the University Human Ethics Committee, best wishes with your research!

Ms Barbara Doherty
Administrative Officer (Research Ethics)
University Human Ethics Committee
Research Compliance Unit / Research Services
La Trobe University Bundoora, Victoria 3086
P: (03) 9479 – 1443 / F: (03) 9479 - 1464
http://www.latrobe.edu.au/research-services/ethics/

The Human Research Ethics Committee operates in accordance with the *NHMRC National Statement on Ethical Conduct in Human Research 2007*

PO Royal Melbourne Hospital
Parkville Victoria 3050
Telephone 61 3 9342 8530
Facsimile 61 3 9342 8548
Email: research@mh.org.au
Website: http://research.mh.org.au
ABN 73 802 706 972

OFFICE FOR RESEARCH

MELBOURNE HEALTH

Research Directorate - Human Ethics Committee Approval Form

Telephone: 9342 8530 Facsimile: 9342 8548

This is to certify that

HREC Project No: 2009.079 **Approval date: 13/01/2010** **Expiry date: 13/01/2013**

Project Title: PrePARE - Prediction and Prevention to Achieve Optimal Recovery Endpoints after stroke

Principal Investigator: Prof. Stephen Davis
Department of Neurology
The Royal Melbourne Hospital
C/- The Post Office
PARKVILLE VIC 3050

Sponsored by: N/A

Protocol No: NTA0902 Version: 2.6 Dated: 30/04/2009

Participant Information and Consent Form: Version 2.0 dated 14/10/2009
Participant Information and Consent Form – Person Responsible: Version 2.0 dated 14/10/2009
Participant Information and Consent To Continue in Research: Version 2.0 dated 14/10/2009

Investigator Brochure: N/A

Other enclosures:(please describe eg advertisement etc.) N/A

Conducted at: Royal Melbourne Hospital **has been approved**

This proposal meets the requirements of the *NHMRC National Statement on Ethical Conduct in Human Research 2007.*

It is now your responsibility to ensure that all people conducting this research project are made aware of which documents have been approved.

This approval is subject to ongoing, current and valid insurance coverage throughout the duration of the conduct of the study.

You are required to notify the Secretary of the Human Research Ethics Committee of

- Any change in the protocol and the reason for that change together with an indication of ethical implications (if any) by submitting an amendment to the study.
- Serious adverse effects on subjects and the action taken to manage them, including amended Plain Language Statement and Consent Form where appropriate.
- Any unforeseen events.
- Your inability to continue as Principal Investigator, or any other change in research personnel involved in the study
- A delay of more than 12 months in the commencement of the project.
- The actual date of commencement of the study.

You are required to submit to the Human Research Ethics Committee

- An Annual Report every twelve months for the duration of the project.
- A detailed Final Report at the conclusion of the project.

The Human Research Ethics Committee may conduct an audit at any time.

An extension of the project beyond the stated conclusion date should be sought from the Human Research Ethics Committee.

Signed: [redacted]
Dr. Angelli Watt
Secretary – Human Research Ethics Committee

Human Research Ethics Committee
Research Ethics Unit
Henry Buck Building
Austin Hospital

TO:	**Dr Henry Ma** **National Stroke Research Institute** **Repat Campus**
PROJECT:	PREPARE - prediction and prevention to achieve optimal recovery endpoints after stroke.
PROTOCOL NO:	NTA0902
PROJECT NO:	H2010/03588
FROM:	**Ms Jill Davis, Research Ethics Unit Manager**
DATE:	6 January 2010
RE:	**Protocol Version 2.6 dated 30 April 2009** **Participant Information and Consent Form Version 1.2 dated 22 December 2009** **Person Responsible Information and Consent Form Version 1.2 dated 22 December 2009** **Continuing in Research Care Participant Information and Consent Form Version 1.1 dated 30 June 2009**
Approval Period:	**6 January 2010 to 6 January 2013**

Agenda Item: 5.2

Further to my letter dated 27 August 2009 concerning the above detailed project, I am writing to acknowledge that your response to the issues raised by the Human Research Ethics Committee at their meeting on 20 August 2009 is satisfactory. This project now has full ethical approval for a period of three years from the date of this letter.

Before the study can commence you must ensure that you have:

- A signed Clinical Trial Agreement
- Signed indemnities
- A copy of the CTN acknowledgment from the TGA. Please note a copy of the acknowledgement is to be forwarded to the Research Ethics Unit.
- For trials involving radiation it is your responsibility to ensure the research is added to the Austin Health Management Licence issued by Department of Human Services – Radiation Safety Section prior to study commencement should it be required (check your Medical Physicist Report). The HREC must be notified when the research has been added to the licence.
- It is a requirement that a progress report is submitted to the Committee annually, or more frequently as directed. Please note a final report must be

submitted for all studies. Should you plan for your study to go beyond the 3-year ethics approval, please request in writing an extension of ethics approval prior to its lapsing. If your study will not commence within 12 months, a request must be forwarded to the HREC justifying the delay beyond 12 months. Should such a request not be received, ethics approval will lapse and a resubmission to the HREC will then be necessary.

- Any changes to the original application will require a submission of a protocol amendment for consideration as this approval only relates to the original application as detailed above.
- Please notify the HREC of any changes to research personnel. All new investigators must be approved prior to performing any study related activities.
- It is now your responsibility to ensure that all people (i.e. all investigators, sponsor and other relevant departments in the hospital) associated with this particular study are made aware of what has been approved.

The Committee wishes to be informed as soon as practicable of any untoward effects experienced by any participant in the trial where those effects in degree or nature were not anticipated by the researchers. The HREC has adopted the NHMRC Australian Health Ethics Committee (AHEC) Position Statement 'Monitoring and reporting of safety for clinical trials involving therapeutic products' May 2009

DETAILS OF ETHICS COMMITTEE:
It is the policy of the Committee not to release personal details of its members. However I can confirm that at the meeting at which the above project was considered, the Committee fulfilled the requirements of the National Health and Medical Research Council in that it contained men and women encompassing different age groups and included people in the following categories:

Chairperson
Ethicist
Lawyer
Lay Man
Lay Woman
Person fulfilling a Pastoral Care Role
Person with Counselling Experience
Person with Research Experience

Additional members include:

- Chairs of all sub committees, or nominees
- Other persons as considered appropriate for the type/s of research usually being considered

I confirm that the Principal Investigator or Co-Investigators were not involved in the approval of this project. I further confirm that all relevant documentation relating to this study is kept on the premises of Austin Health for more than three years.

The Committee is organised and operates according to the National Statement on Ethical Conduct in Human Research (NHMRC The National Statement) and the Note for Guidance on Good Clinical Research Practice (CPMP/ICH/135/95) annotated with TGA comments (July 2008) and the applicable laws and regulations; and the Health Privacy Principles in The Health Records Act 2001.

Appendix F

Modified Rankin Scale (mRS) (Bonita & Beaglehorn, 1988)

Grade	Description
0	No symptoms
1	No significant disability, despite symptoms: able to undertake all usual duties and activities
2	Slight disability: able to look after own affairs without assistance, but unable to perform all previous activities
3	Moderate disability: requires some help, but able to walk unassisted
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Appendix G

Patient Health Questionnaire (PHQ-2) (Kroenke et al., 2003)

Stem Question	Item	Construct
Over the last two weeks, how often have you been bothered by any of the following problems?	1. Little interest or pleasure in doing things	Anhedonia
	2. Feeling down, depressed, or hopeless	Low mood

Note. Each item scored as follows: 0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day.

Appendix H

Charlson Comorbidity Index (CCI): Medical Conditions and their Associated Weighted Score (Charlson et al., 1987)

Comorbidity	Charlson adjusted severity weights [a]
Acquired Immune Deficiency Syndrome (AIDS)	6
Connective tissue disease	1
Cerebrovascular disease	1
Chronic pulmonary disease	1
Congestive heart failure	1
Dementia	1
Diabetes mellitus [b]	
Diabetes mellitus without end organ damage	1
Diabetes mellitus with organ damage	2
Hemiplegia	2
Leukaemia	2
Liver disease [b]	
Mild liver disease	1
Moderate or severe liver disease	3
Malignant lymphoma	2
Myocardial infarct	1
Ulcer disease	1
Peripheral vascular disease	1
Renal disease	
Renal calculi or mild renal disease	0
Moderate or severe renal disease	2
End stage renal disease	3
Solid tumour [b]	
Non-metastatic tumour	2
Metastatic tumour	6

Note. [a] The weighted score received if the medical condition was present. A score of 0 was assigned if the medical condition was not present. [b] The medical condition was coded as separate variables in the original version of the index.

Appendix I

National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989)

Item	Sub-item	Description	Score range
1	1a	Level of consciousness	0-3
	1b	Level of consciousness – questions	0-2
	1c	Level of consciousness – commands	0-2
2		Extraocular movements	0-2
3		Vision (no visual loss, partial, complete or bilateral hemianopia)	0-3
4		Facial weakness (normal, minor partial or complete paralysis)	0-3
5	5a	Motor arm – left (strength and drift)	0-4
	5b	Motor arm – right (strength and drift)	0-4
6	6a	Motor leg – left (strength and drift)	0-4
	6b	Motor leg – right (strength and drift)	0-4
7		Limb coordination (normal, ataxia in one or two limbs)	0-2
8		Sensory loss (normal, mild to moderate, severe to total loss)	0-2
9		Aphasia (no aphasia, mild to moderate aphasia, severe aphasia)	0-3
10		Dysarthria (normal, mild to moderate, severe)	0-2
11		Extinction and inattention	0-2

Appendix J

Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979)

Item and description	Score range
Apparent sadness Despondency, gloom, and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture; rate by depth and inability to brighten up	0-6
Reported sadness Reports of depressed mood, regardless of whether it is reflected in appearance or not; includes low spirits, despondency, or the feeling of being beyond help and without hope	0-6
Inner tension Feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish; rate by intensity, frequency, duration, and extent of reassurance called for	0-6
Reduced sleep Experience of reduced duration or depth of sleep compared to the patient's own normal pattern when well	0-6
Reduced appetite Feeling of loss of appetite; rate by loss of desire for food or the need to force oneself to eat	0-6
Concentration difficultly Difficulties in collecting one's thoughts mounting to incapacitating lack of concentration; rate by intensity, frequency, and degree of incapacity produced	0-6
Lassitude Difficulty getting started or slowness initiating and performing everyday activities	0-6
Inability to feel Subjective experience of reduced interest in the surroundings or activities that normally give pleasure; the ability to react with adequate emotion to circumstances or people is reduced	0-6
Pessimistic thoughts Thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin	0-6
Suicidal thoughts Feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide; suicidal attempts should not in themselves influence the rating	0-6

Note. Intermediate points (1, 3 and 5) on this scale are available are also available for selection and are denoted as the previous description and 'worsening symptoms'.

Appendix K

Structured Interview Guide for Montgomery-Åsberg Depression Rating Scale (MADRS SIGMA) (Williams & Kobak, 2008)

Structured Interview Guide for the Montgomery–Åsberg Depression Rating Scale (SIGMA)

PT'S INITIALS: _____ PT'S ID: _____ INTERVIEWER: _____ TIME BEGAN SIGMA: _____ DATE: _____

OVERVIEW: I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUT-PATIENT: Have you been working? (What kind of work do you do?) IF NOT: Why not?

In the past week, have you been feeling sad or unhappy? (Depressed at all?) IF YES: Can you describe what this has been like for you?
(IF UNKNOWN: How bad has that been?)
IF DEPRESSED: Does the feeling lift at all if something good happens
How much does your mood lift? Does the feeling ever go away completely? (What things have made you feel better?)
How often did you feel (depressed/OWN EQUIVALENT) this past week? (IF UNKNOWN: How many days this week did you feel that way? How much of each day?)
In the past week, how have you been feeling about the future? (Have you been discouraged or pessimistic?) What have your thoughts been? How (discouraged or pessimistic) have you been? How often have you felt that way? Do you think things will ever get better for you?
IF ACKNOWLEDGES DEPRESSED MOOD, TO GET CONTEXT ASK:
How long have you been feeling this way?

1. REPORTED SADNESS. Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances
1
2 Sad or low but brightens up without difficulty
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances
5
6 Continuous or unvarying sadness, misery or despondency

RATING BASED ON OBSERVATION DURING INTERVIEW AND THE FOLLOWING QUESTIONS.
In the past week, do you think you have looked sad or depressed to other people? Did anyone say you looked sad or down?
How about when you've looked in the mirror? Did you look gloomy or depressed?
IF YES: How sad or depressed do you think you have looked?
How much of the time over the past week do you think you have looked depressed or down?
IF APPEARANCE WAS DEPRESSED IN PAST WEEK: Have you been able to laugh or smile at all during the past week? IF YES: How hard has it been for you to laugh or smile, even if you weren't feeling happy inside?

2. APPARENT SADNESS. Representing despondency, gloom and despair. (More than just ordinary transient low spirits) reflected in speech, facial expressions and posture. Rate by depth and inability to brighten up.

0 No sadness
1
2 Looks dispirited but does brighten up without difficulty
3
4 Appears sad and unhappy most of the time
5
6 Looks miserable all the time. Extremely despondent

Have you felt tense or edgy in the past week? Have you felt anxious or nervous?
IF YES: Can you describe what that has been like for you? How bad has it been? (Have you felt panicky?)
What about feeling fearful that something bad is about to happen?
How hard has it been to control these feelings? (What has it taken to help you feel calmer? Has anything worked to calm you down?)
How much of the time have you felt this way over the past week?

3. INNER TENSION. Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension
1
2 Occasional feelings of edginess and ill-defined discomfort
3
4 Continuous feelings of inner tension or intermittent panic which the patient can master with some difficulty
5
6 Unrelenting dread or anguish. Overwhelming panic

How has your sleeping been in the past week? (How many hours have you been sleeping, compared with usual?)

Have you had trouble falling asleep? (How long has it been taking you to fall asleep this past week?)

Have you been able to stay asleep through the night? (Have you been waking up at all in the middle of the night? How long does it take you to go back to sleep?)

Has your sleeping been restless or disturbed?

4. REDUCED SLEEP. Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual
1
2 Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep
3
4 Sleep reduced or broken by at least 2 hours
5
6 Less than 2 or 3 hours sleep

How has your appetite been this past week?
(What about compared with your usual appetite?)
Have you been less interested in food? (How much less?)
Does food taste as good as usual? IF LESS: How much less?
Have you had to force yourself to eat?
Have other people had to urge you to eat?

5. REDUCED APPETITE. Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite
1
2 Slightly reduced appetite
3
4 No appetite. Food is tasteless
5
6 Needs persuasion to eat at all

Appendix (continued)

Have you had trouble concentrating or collecting your thoughts in the past week? (How about at home or at work?) IF YES: Can you give me some examples? (Have you been able to concentrate on reading a newspaper or magazine? Do you need to read things over and over again?)

How often has that happened in the past week? Has this caused any problems for you? IF YES: Can you give me some examples?

Has your trouble concentrating been so bad at any time in the past week that it has been difficult to follow a conversation? (IF YES: How bad has that been? How often has that happened this past week?)

NOTE: ALSO CONSIDER BEHAVIOUR DURING INTERVIEW.

6. CONCENTRATION DIFFICULTIES. Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentration
1
2 Occasional difficulties in collecting one's thoughts
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation
5
6 Unable to read or converse without great difficulty

Have you had any trouble getting started at things in the past week? IF YES: What things?

Have you had to push yourself to do things? IF YES: What things? How hard have you had to push yourself? Are you OK once you get started or is it still more of an effort to get something done? What about getting started at simple routine everyday things (like getting dressed)?

Have you done everyday things more slowly than usual? (Have you been sluggish?) IF YES: Like what, for example? How bad has that been?

7. LASSITUDE. Representing a difficulty getting started, or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness
1
2 Difficulties in starting activities
3
4 Difficulties in simple routine activities, which are carried out with effort
5
6 Complete lassitude. Unable to do anything without help

Have you been less interested in things around you, or in activities you used to enjoy? IF YES: What things? How bad has that been? How much less interested in (those things) are you now compared with before?

Have you been less able to enjoy the things you usually enjoy? Has there been any change in your ability to feel emotions? (Do you feel things less intensely than you used to, things like anger, grief, pleasure?) IF YES: Can you tell me more about that? (IF UNKNOWN: Are you able to feel any emotions at all?)

How do you feel towards your family and friends? Is that different from usual? IF REDUCED: Do you feel less than you used to towards them?

8. INABILITY TO FEEL. Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people
1
2 Reduced ability to enjoy usual interests
3
4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances
5
6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure, and a complete or even painful failure to feel for close relatives and friends

Have you been putting yourself down, or feeling that you're a failure in some way, over the past week? (Have you been blaming yourself for things that you've done, or not done?) IF YES: What have your thoughts been? How often have you felt that way?

Have you been feeling guilty about anything in the past week? What about feeling as if you have done something bad or sinful? IF YES: What have your thoughts been? How often have you felt that way?

ALSO CONSIDER RESPONSES TO QUESTIONS ABOUT PESSIMISM FROM ITEM 1.

9. PESSIMISTIC THOUGHTS. Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts
1
2 Fluctuating ideas of failure, self-reproach or self-depreciation
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future
5
6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakeable

This past week, have you felt like life isn't worth living? IF YES: Tell me about that. IF NO: What about feeling as if you're tired of living?

This week, have you thought that you would be better off dead? IF YES: Tell me about that.

Have you had thoughts of hurting or even killing yourself this past week? IF YES: What have you thought about? How often have you had these thoughts? How long have they lasted? Have you actually made plans? IF YES: What are these plans? Have you made any preparations to carry out these plans? (Have you told anyone about it?)

10. SUICIDAL THOUGHTS. Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparation for suicide. Suicidal attempts should not in themselves influence this rating.

0 Enjoys life or takes it as it comes
1
2 Weary of life. Only fleeting suicidal thoughts
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide

TOTAL MADRS SCALE SCORE: _____

Appendix L

Stroke Impact Scale (SIS) (Duncan et al., 2003a)

The purpose of this questionnaire is to evaluate how stroke has impacted your health and life. We want to know from **your point of view** how stroke has affected you. We will ask you questions about impairments and disabilities caused by your stroke, as well as how stroke has affected your quality of life. Finally, we will ask you to rate how much you think you have recovered from your stroke.

These questions are about the physical problems which may have occurred as a result of your stroke.

1. In the past week, how would you rate the strength of your...	**A lot of strength**	**Quite a bit of strength**	**Some strength**	**A little strength**	**No strength at all**
a. Arm that was most affected by your stroke?	5	4	3	2	1
b. Grip of your hand that was most affected by your stroke?	5	4	3	2	1
c. Leg that was most affected by your stroke?	5	4	3	2	1
d. Foot/ankle that was most affected by your stroke?	5	4	3	2	1

These questions are about your memory and thinking.

2. In the past week, how difficult was it for you to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
a. Remember things that people just told you?	5	4	3	2	1
b. Remember things that happened the day before?	5	4	3	2	1
c. Remember to do things (e.g. keep scheduled appointments or take medication)?	5	4	3	2	1
d. Remember the day of the week?	5	4	3	2	1
e. Concentrate?	5	4	3	2	1
f. Think quickly?	5	4	3	2	1
g. Solve everyday problems?	5	4	3	2	1

These questions are about how you feel, about changes in your mood and about your ability to control your emotions since your stroke.

3. In the past week, how often did you...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Feel sad?	5	4	3	2	1
b. Feel that there is nobody you are close to?	5	4	3	2	1
c. Feel that you are a burden to others?	5	4	3	2	1
d. Feel that you have nothing to look forward to?	5	4	3	2	1
e. Blame yourself for mistakes that you made?	5	4	3	2	1
f. Enjoy things as much as ever? [a]	5	4	3	2	1
g. Feel quite nervous?	5	4	3	2	1
h. Feel that life is worth living? [a]	5	4	3	2	1
i. Smile and laugh at least once a [a] day?	5	4	3	2	1

Note. [a] item changes polarity; that is, when manually scored these items require reverse scoring.

The following questions are about your ability to communicate with other people, as well as your ability to understand what you read and what you hear in a conversation.

4. In the past week, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Extremely difficult
a. Say the name of someone who was in front of you?	5	4	3	2	1
b. Understand what was being said to you in a conversation?	5	4	3	2	1
c. Reply to questions?	5	4	3	2	1
d. Correctly name objects?	5	4	3	2	1
e. Participate in a conversation with a group of people?	5	4	3	2	1
f. Have a conversation on the telephone?	5	4	3	2	1
g. Call another person on the telephone, including selecting the correct phone number and dialling?	5	4	3	2	1

The following questions ask about activities you might do during a typical day.

5. In the past 2 weeks, how difficult was it to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Could not do at all**
a. Cut your food with a knife and fork?	5	4	3	2	1
b. Dress the top part of your body?	5	4	3	2	1
c. Bathe yourself?	5	4	3	2	1
d. Clip your toenails?	5	4	3	2	1
e. Get to the toilet on time?	5	4	3	2	1
f. Control your bladder (not have an accident)?	5	4	3	2	1
g. Control your bowels (not have an accident)?	5	4	3	2	1
h. Do light household tasks/chores (e.g. dust, make a bed, take out garbage, do the dishes)?	5	4	3	2	1
i. Go shopping?	5	4	3	2	1
j. Do heavy household chores (e.g. vacuum, laundry or yard work)?	5	4	3	2	1

The following questions are about your ability to be mobile, at home and in the community.

6. In the past 2 weeks, how difficult was it to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Could not do at all**
a. Stay sitting without losing your balance?	5	4	3	2	1
b. Stay standing without losing your balance?	5	4	3	2	1
c. Walk without losing your balance?	5	4	3	2	1
d. Move from a bed to a chair?	5	4	3	2	1
e. Walk one block?	5	4	3	2	1
f. Walk fast?	5	4	3	2	1
g. Climb one flight of stairs?	5	4	3	2	1
h. Climb several flights of stairs?	5	4	3	2	1
i. Get in and out of a car?	5	4	3	2	1

The following questions are about your ability to use your hand that was most affected by your stroke.

7. In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Could not do at all**
a. Carry heavy objects (e.g. bag of groceries)?	5	4	3	2	1
b. Turn a doorknob?	5	4	3	2	1
c. Open a can or jar?	5	4	3	2	1
d. Tie a shoe lace?	5	4	3	2	1
e. Pick up a dime?	5	4	3	2	1

The following questions are about how stroke has affected your ability to participate in the activities that you usually do, things that are meaningful to you and help you to find purpose in life.

8. During the past 4 weeks, how much of the time have you been limited in...	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
a. Your work (paid, voluntary or other)	5	4	3	2	1
b. Your social activities?	5	4	3	2	1
c. Quiet recreation (crafts, reading)?	5	4	3	2	1
d. Active recreation (sports, outings, travel)?	5	4	3	2	1
e. Your role as a family member and/or friend?	5	4	3	2	1
f. Your participation in spiritual or religious activities?	5	4	3	2	1
g. Your ability to control your life as you wish?	5	4	3	2	1
h. Your ability to help others?	5	4	3	2	1

Appendix M

Stroke Impact Scale 16 (SIS-16) (Duncan et al., 2003b)

In the past 2 weeks, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Dress the top part of your body?	5	4	3	2	1
b. Bathe yourself?	5	4	3	2	1
c. Get to the toilet on time?	5	4	3	2	1
d. Control your bladder (not have an accident)?	5	4	3	2	1
e. Control your bowels (not have an accident)?	5	4	3	2	1
f. Stand without losing balance?	5	4	3	2	1
g. Go shopping?	5	4	3	2	1
h. Do heavy household chores (e.g. vacuum, laundry or yard work)?	5	4	3	2	1
i. Stay sitting without losing your balance?	5	4	3	2	1
j. Walk without losing your balance?	5	4	3	2	1
k. Move from a bed to a chair?	5	4	3	2	1
l. Walk fast?	5	4	3	2	1
m. Climb one flight of stairs?	5	4	3	2	1
n. Walk one block?	5	4	3	2	1
o. Get in and out of a car?	5	4	3	2	1
p. Carry heavy objects (e.g. bag of groceries) with your affected hand?	5	4	3	2	1

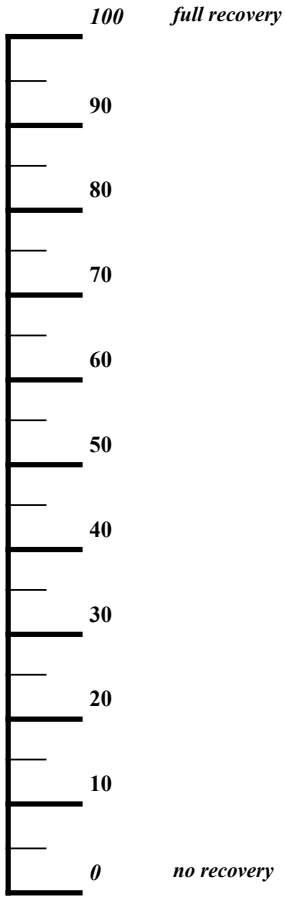
Appendix N

Stroke Impact Scale 16 (SIS-16) and Corresponding Item and Domain in SIS 3.0

SIS-16 Items	Corresponding item and domain from the SIS 3.0
Question stem: *In the past 2 weeks, how difficult was it to:*	
1. Dress the top part of your body?	5b. Activities of daily living
2. Bathe yourself?	5c. Activities of daily living
3. Get to the toilet on time?	5e. Activities of daily living
4. Control your bladder (not have an accident)?	5f. Activities of daily living
5. Control your bowels (not have an accident)?	5g. Activities of daily living
6. Stand without losing balance?	6b. Mobility
7. Go shopping?	5i. Activities of daily living
8. Do heavy household chores (for example: laundry or gardening)?	5j. Activities of daily living
9. Stay sitting without losing your balance?	6a. Mobility
10. Walk without losing your balance?	6c. Mobility
11. Move from a bed to a chair?	6d. Mobility
12. Walk fast?	6f. Mobility
13. Climb one flight of stairs?	6g. Mobility
14. Walk one block?	6e. Mobility
15. Get in and out of a car?	6i. Mobility
16. Carry heavy objects (for example: groceries) with your affected hand?	7a. Hand function

Appendix O

Stroke Impact Scale Visual Analogue Scale (SIS VAS) (Duncan et al. 2003)



Appendix P

Work Social and Adjustment Scale (WSAS) (Mundt et al., 2002)

Stem	Item	Domain
Because of my stroke…	1	My ability to work is impaired.
	2	My home management (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired.
	3	My social leisure activities (with other people e.g., parties, bars, clubs, outings, visits, dating, home entertainment) are impaired.
	4	My private leisure activities (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired.
	5	My ability to form and maintain close relationships with others, including those I live with this, is impaired.

Note. Each item scored as follows: 0 = not at all, 2 = slightly, 4 = definitely, 6 = markedly, 8 = very severely. Intermediate points (1, 3, 5 and 7) on this scale are also available for selection.

Appendix Q

Barthel Index (BI) (Mahoney & Barthel, 1965)

Item	Scoring
1. Bowels	0 = incontinent (or needs to be given enema) 1 = occasional accident (once per week) 2 = continent
2. Bladder	0 = incontinent, or catheterised and unable to manage 1 = occasional accident (maximum: once per day) 2 – continent (for over 7 days)
3. Grooming	0 = needs help with personal care 1 = independent with face, hair teeth, shaving (implements provided)
4. Toilet use	0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
5. Feeding	0 = unable 1 = needs help cutting, spreading butter, etc. 2 = independent (food provided within reach)
6. Transfer	0 = unable – no sitting balance 1 = major help (one or two people, physical) cat sit 2 = minor help (verbal or physical) 3 = independent
7. Mobility	0 = immobile 1 = wheelchair independent, including corners 2 = walks with help of one person (verbal or physical) 3 – independent (but may use any aid)
8. Dressing	0 = dependent 1 = needs help, but can do about half unaided 2 = independent (including buttons, zips, laces)
9. Stairs	0 = unable 1 = needs help 2 = independent
10. Bathing	0 = dependent 1 = independent

Appendix R

Stata Code for Inferential Statistics

Random Effects Logistic Regression

Empirical Research Study 1, presented in Chapter 5

```
. xtlogit depress_status i.timepoint, or i(participant)

Fitting comparison model:

Iteration 0:   log likelihood = -284.82396
Iteration 1:   log likelihood = -283.92589
Iteration 2:   log likelihood = -283.92561
Iteration 3:   log likelihood = -283.92561

Fitting full model:

tau =  0.0     log likelihood = -283.92561
tau =  0.1     log likelihood = -280.60468
tau =  0.2     log likelihood = -277.36189
tau =  0.3     log likelihood = -274.22764
tau =  0.4     log likelihood = -271.25381
tau =  0.5     log likelihood = -268.53579
tau =  0.6     log likelihood = -266.26224
tau =  0.7     log likelihood = -264.84653
tau =  0.8     log likelihood = -265.37748

Iteration 0:   log likelihood =  -264.8503
Iteration 1:   log likelihood = -263.87246
Iteration 2:   log likelihood = -263.87041
Iteration 3:   log likelihood = -263.87041

Random-effects logistic regression              Number of obs     =        426
Group variable: participant                     Number of groups  =        142

Random effects u_i ~ Gaussian                   Obs per group:
                                                              min =          3
                                                              avg =        3.0
                                                              max =          3

Integration method: mvaghermite                 Integration pts.  =         12

                                                Wald chi2(2)      =       2.65
Log likelihood  = -263.87041                    Prob > chi2       =     0.2655

------------------------------------------------------------------------------
depress_status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
     Timepoint |
           2   |   1.301895   .3872141     0.89   0.375     .7267896    2.332079
           3   |   .7973649   .2404899    -0.75   0.453      .441499    1.440073
               |
         _cons |   .4984285   .1318569    -2.63   0.008      .296771    .8371134
---------------+--------------------------------------------------------------
      /lnsig2u |   1.087564   .3245886                      .4513818    1.723746
---------------+--------------------------------------------------------------
       sigma_u |   1.722509   .2795534                      1.253188    2.367591
           rho |    .474202   .0809311                       .323121    .6301588
------------------------------------------------------------------------------
Note: Estimates are transformed only in the first equation.
Note: _cons estimates baseline odds (conditional on zero random effects).
LR test of rho=0: chibar2(01) = 40.11                  Prob >= chibar2 = 0.000
```

```
. xtlogit depress_status ib(2).timepoint, or i(participant)

Fitting comparison model:

Iteration 0:   log likelihood = -284.82396
Iteration 1:   log likelihood = -283.92589
Iteration 2:   log likelihood = -283.92561
Iteration 3:   log likelihood = -283.92561

Fitting full model:

tau =  0.0     log likelihood = -283.92561
tau =  0.1     log likelihood = -280.60468
tau =  0.2     log likelihood = -277.36189
tau =  0.3     log likelihood = -274.22764
tau =  0.4     log likelihood = -271.25381
tau =  0.5     log likelihood = -268.53579
tau =  0.6     log likelihood = -266.26224
tau =  0.7     log likelihood = -264.84653
tau =  0.8     log likelihood = -265.37748

Iteration 0:   log likelihood =  -264.8503
Iteration 1:   log likelihood = -263.87246
Iteration 2:   log likelihood = -263.87041
Iteration 3:   log likelihood = -263.87041

Random-effects logistic regression              Number of obs     =        426
Group variable: participant                     Number of groups  =        142

Random effects u_i ~ Gaussian                   Obs per group:
                                                              min =          3
                                                              avg =        3.0
                                                              max =          3

Integration method: mvaghermite                 Integration pts.  =         12

                                                Wald chi2(2)      =       2.65
Log likelihood  = -263.87041                    Prob > chi2       =     0.2655

------------------------------------------------------------------------------
depress_status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
     timepoint |
           1   |    .768111   .2284542    -0.89   0.375     .4288019    1.375914
           3   |   .6124648   .1847101    -1.63   0.104     .3391343     1.10609
               |
         _cons |   .6489017      .1679    -1.67   0.095     .3907822    1.077514
---------------+--------------------------------------------------------------
      /lnsig2u |   1.087564   .3245886                      .4513818    1.723746
---------------+--------------------------------------------------------------
       sigma_u |   1.722509   .2795534                      1.253188    2.367591
           rho |    .474202   .0809311                       .323121    .6301588
------------------------------------------------------------------------------
Note: Estimates are transformed only in the first equation.
Note: _cons estimates baseline odds (conditional on zero random effects).
LR test of rho=0: chibar2(01) = 40.11                  Prob >= chibar2 = 0.000
```

Quantile Regression

Empirical Research Study 2, presented in Chapter 7

```
global xlist gender nihss_score age madrs_3m
global ylist sis_index_3m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age madrs_12m
global ylist sis_index_12m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age madrs_3m
global ylist sis_vas_3m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age madrs_12m
global ylist sis_vas_12m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age madrs_3m
global ylist wsas_3m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age madrs_12m
global ylist wsas_12m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age madrs_3m
global ylist bi_3m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age madrs_12m
global ylist bi_12m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)
```

Quantile Regression

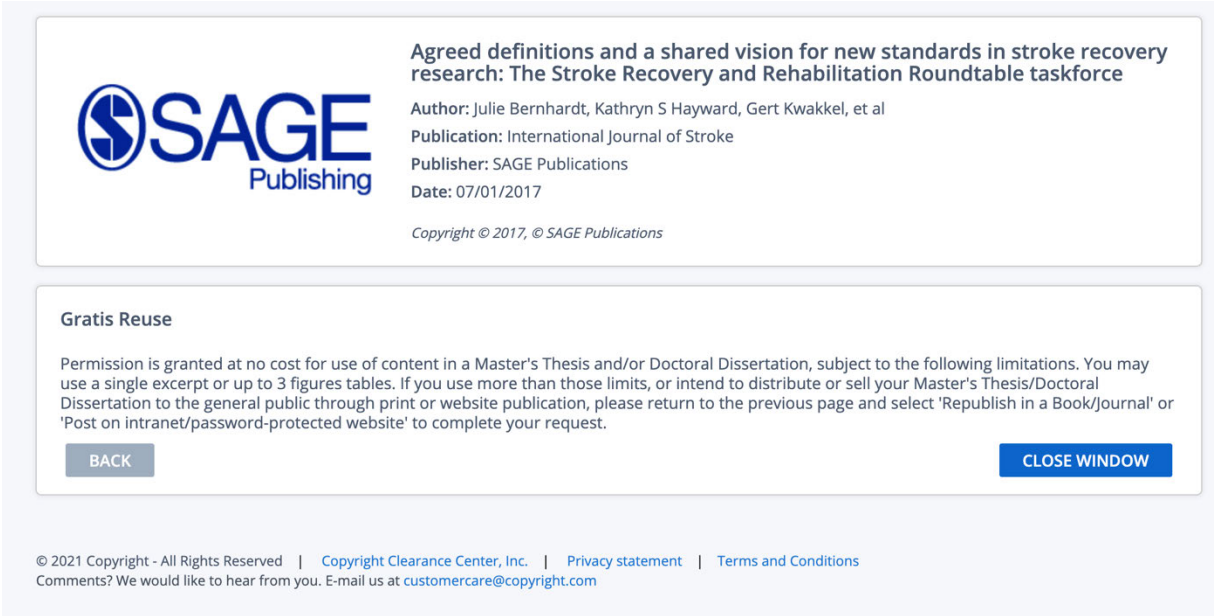
Empirical Research Study 3, presented in Chapter 8

```
global xlist gender nihss_score age cci_score
global ylist sis_index_3m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age cci_score
global ylist sis_index_12m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age cci_score
global ylist sis_vas_3m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)

global xlist gender nihss_score age cci_score
global ylist sis_vas_12m
sum $xlist $ylist
qreg $ylist $xlist, quantile (.25)
qreg $ylist $xlist
qreg $ylist $xlist, quantile (.75)
```

Appendix S

Permissions

Automated permission to use Figure 1 from Bernhardt et al. (2017) in this dissertation [Figure 2.2 (Chapter 2) and Figure 3.1 (Chapter 3)] was granted by SAGE publishing.



SAGE Publishing

Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce

Author: Julie Bernhardt, Kathryn S Hayward, Gert Kwakkel, et al

Publication: International Journal of Stroke

Publisher: SAGE Publications

Date: 07/01/2017

Copyright © 2017, © SAGE Publications

Gratis Reuse

Permission is granted at no cost for use of content in a Master's Thesis and/or Doctoral Dissertation, subject to the following limitations. You may use a single excerpt or up to 3 figures tables. If you use more than those limits, or intend to distribute or sell your Master's Thesis/Doctoral Dissertation to the general public through print or website publication, please return to the previous page and select 'Republish in a Book/Journal' or 'Post on intranet/password-protected website' to complete your request.

BACK CLOSE WINDOW

Permission to use the Perspective Article (presented in Chapter 6) in this dissertation was approved by the Senior Publishing Coordinator at the Medical Journal of Australia via email correspondence, 12 August 2021.

Dear Katherine

As owners of copyright for material published in the Medical Journal of Australia (MJA), we grant you a non-exclusive licence to use the material described in your email below in your thesis, subject to the conditions below.

This permission is conditional on all intended publications fully acknowledging the MJA as the original source of the content in the following manner:

Sewell K, Tse T, Donnan GA, et al. Screening for Post-Stroke Depression – Who, When and How?. *Med J Aust* 2021; in press. © Copyright 2021. *The Medical Journal of Australia*. Reproduced with permission.

Could you please confirm your acceptance of these terms by return email?

Kind regards
Kerrie

Kerrie Harding
Sen or Pub sh ng Coord nator
The Med ca Journa of Austra a

Suite 1 Level 19 456 Kent St Sydney NSW 2000
Locked Bag 3030 Strawberry Hills NSW 2012
Email mja@mja com au and kharding@mja com au
Direct +61 2 9562 6640
Fax +61 2 9562 6600

Journal mpact Factor 7 74 (Clarivate Analytics 2020)