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Psychological Problems in Stroke: Prevalence, Risk Factors, and Assessment in the Pre-stroke State.

A Thesis by

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Submitted for the degree of Doctor of Philosophy

To

The University of Glasgow

From

The Institute of Cardiovascular and Medical Sciences

College of Medical, Veterinary and Life Sciences

University of Glasgow

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Abstract

Background: The psychological impact of stroke is well recognised as being of clinical importance. Historically, this field has received less attention than the physical consequences of stroke, but work designed to develop our understanding of post-stroke psychology is now well underway. Much of the current research of post-stroke psychology is overly limited however; little attention has been paid to the potential impact of the pre-stroke state on post-stroke psychology. As a consequence, fundamental information in relation to the pre-stroke state is lacking, ranging from the prevalence and relevant risk associations of various psychological and physical conditions, to the validity and optimal use of pre-stroke state assessment methods. The purpose of this thesis is to improve our understanding of the pre-stroke state in relation to these under-researched areas.

Method: I conducted a series of studies designed to improve our understanding of the pre-stroke state in the areas of prevalence, risk association, and method of assessment. Specifically, I conducted a diagnostic test accuracy study to evaluate the psychometric properties of two informant questionnaires that can be used to assess pre-stroke cognition: the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) and Acquired Dementia 8 (AD8).

I conducted a systematic review and meta-analyses to establish pre-stroke depression prevalence and investigate its association with post-stroke depression. Based on the findings of this, I explored the potential use of informant tools for pre-stroke depression assessment by comparing the diagnostic test accuracy of the Stroke Aphasic Depression Questionnaire (SADQ) against the Geriatric Depression Scale (GDS), and the diagnostic test accuracy of the best performing informant questionnaire against that of medical records.

I conducted secondary analysis of existing data held in two databases to investigate pre-stroke functioning and pre-stroke frailty. The Anglia Stroke Clinical Network Evaluation Study database was utilised to assess the validity of the pre-stroke modified Rankin Scale (mRS) as a measure of function and explore if reported predictive validity of the tool could be influenced by differences in

post-stroke care pathway. The Glasgow Royal Infirmary research database was used to investigate the prevalence of pre-stroke frailty, the validity of a Frailty Index for pre-stroke frailty assessment, and a risk association between pre-stroke frailty and acute post-stroke cognition.

Findings: I found that the IQCODE and AD8 are valid tools for assessing pre-stroke cognition. However, when utilised at recommended published cut-points the IQCODE is more specific, while the AD8 is more sensitive to cognitive impairment. There is also potential that application of differing cut-points could improve performance when used in a pre-stroke context.

My systematic review and meta-analysis suggested that pre-stroke depression prevalence is around 17% and its presence significantly increases odds of post-stroke depression. In addition, there is evidence that the most commonly used method to assess pre-stroke depression, patient medical records, is likely to lack sensitivity to pre-stroke depression.

I explored the use of the SADQ and GDS informant tools for assessment of pre-stroke depression. I found that both tools are valid measures of pre-stroke depression, but the GDS has favourable diagnostic test accuracy properties in comparison to the SADQ; comparative test accuracy performance with medical records is inconclusive, but seems to favour the GDS.

Pre-stroke mRS evaluation suggests it has moderate validity as a measure of pre-stroke functioning and has predictive validity that could not be accounted for by differences in care pathway.

Pre-stroke frailty prevalence is around 28%, rising to ~80% if the pre-frailty state is considered, and the Frailty Index is a valid measure of pre-stroke frailty that can be completed in almost all stroke patients. Pre-stroke frailty also has an association with lower acute post-stroke cognition that is independent of other established risk factors.

Conclusions: In conclusion these findings develop our overall understanding of the pre-stroke state. The IQCODE and AD8 are both valid tools for assessment of

pre-stroke cognition; however, they demonstrate contrasting strengths when employed at their recommended cut-points and these cut-points may not be the most optimal when these tools are utilised for pre-stroke assessment.

Pre-stroke depression appears prevalent, existing in around one in six stroke patients, and it increases the odds of patients experiencing post-stroke depression. It is possible that informant assessment for detection of pre-stroke depression can outperform patient medical records and the GDS appears to outperform the SADQ in the pre-stroke context; however further work is required to confirm this.

The pre-stroke mRS is a valid measure of function but has only moderate validity overall and may not be ideally suited to assessment of function in a pre-stroke context. Pre-stroke frailty may exist in around one quarter of stroke patients, and utilisation of a Frailty index approach appears to be valid. The presence of pre-stroke frailty may also contribute to the poor cognitive performance often observed in patients following acute stroke based on an independent association with lower cognitive performance; hence identification of pre-stroke frailty could be of importance to our understanding of post-stroke psychology.

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Preface: Background and thesis outline

The epidemiology and impact of stroke

Stroke is a major cause of adult disability in both Europe and the United States of America. The UK alone has over 1.2 million stroke survivors with around 100,000 strokes occurring per annum. (1)

The majority (59%) of strokes occur in older adults; however, around a quarter of strokes happen in people of working age. (2) Indeed, over a third (38%) of first-time strokes occur in adults between the ages of 40 to 69 and first-time strokes now occur at an earlier age in comparison to 10 years ago. Between 2007-2016, the average age of stroke occurrence declined from 71 to 68 years for males and 75 to 73 years for females. (3)

Stroke is often not a singular event. One in four stroke patients experience a second stroke within 5 years (4) and 1 in 20 have another stroke while still in hospital. (5) Further strokes typically exacerbate the consequences patients experience, and regularly result in death.

Stroke is suggested to be the second most common cause of death, constituting 10% of all deaths in the developed world. (6, 7) Forty-thousand stroke-related deaths occur in the UK, each year. Death rates from stroke in women are twice that seen from breast cancer. In men, annual deaths from stroke are two times greater than deaths from prostate and testicular cancer combined. (8-10)

However, most patients do not die following stroke. Eighty-five percent of stroke patients in England, Wales and Northern Ireland survive their stay in hospital. (5)

Those who survive stroke experience a broad range of impairments; stroke causes a greater range of disabilities than any other condition. (11) Motor and sensory impairments are among the most commonly recognised: The Stroke

Association's latest State of the Nation report suggests that almost two thirds (65%) of stroke survivors in the UK leave hospital with a disability. (11)

Around three quarters of stroke survivors have arm or leg weakness. (12)

Sixty percent of stroke survivors have visual problems immediately after their stroke; 20% experience visual issues up to three months after stroke. (13)

Around half of all stroke patients have difficulty with swallowing. (12) This can inhibit ability to eat and drink and increases risk of pneumonia. (14)

Around 50% of stroke survivors experience problems with bladder control. (12)

Around a third of stroke survivors experience difficulties with communication due to aphasia. (15)

The presence of these impairments increase pressure on health services. Four out of ten stroke survivors leave hospital requiring help with daily living activities but almost a third receive no social service visits. (5) In Scotland, more than half of stroke survivors need support from other people to be able to walk. (16) Around half of stroke survivors in England, Wales and Northern Ireland require speech and language therapy during their hospital stay. (5)

Estimated stroke costs to the UK are around £9 billion a year as a society. This includes £2.4 billion a year in informal care costs, £1.3 billion in lost income due to care, disability and death, and over £800 million in benefit payments. (17)

There are also costs on a personal level for the stroke patients and their families. Forty-two percent of people report a negative change in their relationship with their partner after a stroke; a quarter state that stroke had a negative impact on their family. (18) Stroke increases the likelihood of unemployment by two to three times in people of working age, up to 8 years after their stroke. (19) Around 1 in 6 stroke survivors experience a loss of

income and almost a third of stroke survivors report increased daily living costs.(18)

The Psychological Impact of Stroke

Consequences of stroke also encompass alterations to patient psychology. (20) Increased emotionalism and issues with fatigue, cognition, anxiety and depression are common.

Stroke survivors and their carers have consistently highlighted the importance of psychological issues. (21) Disorders of psychology have been associated with increased mortality risk (22), impaired daily functioning (23), reduced post-stroke quality of life (24) and adverse effects on rehabilitation engagement. (25) The financial impact of psychological issues in stroke is also substantial. For instance, disorders of depression and mood are expected to cost the National Health Service £3billion per annum by 2026 in England alone. (26)

It has become increasingly apparent in recent years that identification of psychological disorders is essential to our ability to understand the full consequences of a stroke. Once psychological impairments are identified and understood, interventions could be developed with the objective of diminishing their impact upon patient well-being and service costs.

Despite this, the psychological consequences of stroke have traditionally received less attention in research than motor and sensory deficits. Therefore, psychological problems were recently identified as a priority area for stroke research. (27)

Thesis outline

The purpose of this thesis is to enhance our understanding of psychological problems in stroke. This work will focus on two prominent issues of psychology in stroke in particular: cognition and mood.

The opening chapter outlines our current state of knowledge regarding the psychological impact of a stroke in relation to cognition and mood. Chapter 2 discusses the relevance of the largely under-researched pre-stroke state in this context. Our understanding of both psychological and physical pre-stroke conditions that are important to fully comprehend psychological problems in stroke are discussed, before concluding with the specific aims of the thesis. The subsequent chapters describe studies designed to address these aims; and a closing chapter provides a summary and discussion of my overall findings, suggested future directions, and a conclusion.

Acknowledgement

I would like to thank my PhD supervisors, Dr Terry Quinn, Professor Jonathan Evans and Professor David Stott for their supervision, feedback and helpful advice over the last 3 years.

I would also like to thank all of the research nurses who helped recruit and assess patients; the patients who participated in each study; and my funders who provided financial support to make to possible to conduct this work.

A special thanks to Ruth Graham whose recruitment for the APPLE study was essential to the successful completion of that project.

I would like to thank Professor Merete Osler and Dr Terese Jorgensen for providing odds ratio data for my meta-analysis in chapter 4.

Finally, I would like to thank my family for their support and interest in my work throughout the duration of my PhD.

Author's Declaration

My contribution to each chapter of this thesis, along with significant contributions of others involved in each chapter, is outlined below:

Professor Jon Evans, Professor David Stott and Dr Terence Quinn provided supervision, guidance and feedback for each chapter of this thesis.

Preface, chapters 1 and 2: I wrote each of these chapters.

Chapter 3: I wrote the chapter, conducted and interpreted the analysis. I also conducted the clinical interview that was used to establish the pre-stroke gold standard diagnosis. The idea for the study was conceived by Dr Terence Quinn. Recruitment was conducted by the research nurses at the various hospital sites involved. The research nurses also administered the pre-stroke informant questionnaires used in this study.

Chapter 4: I conceived the idea for this review and wrote the chapter. I designed the search strategy and inclusion/exclusion criteria for the study along with my PhD supervisors. Oyiza Momoh and I both conducted the search, data extraction and quality assessment for the papers included in the review. I conducted and interpreted the analysis for the chapter.

Chapter 5: The idea for this study was conceived by Dr Terence Quinn. I wrote the chapter and conducted/interpreted the analysis. As in chapter 3, I conducted the interview that was used to establish the pre-stroke diagnosis and the research nurses were involved in recruitment and administering the pre-stroke informant questionnaires.

Chapter 6: The idea for this study was conceived by Professor Phyo Myint. The analysis was conducted by Dr Allan Clark. I was involved in interpreting the analysis and writing the chapter, along with Dr Terry Quinn.

Chapter 7: Dr Terry Quinn and I conceived the idea for this study. I recruited and assessed the majority of participants for the database utilised in this study. Gillian Cuthbertson contributed substantially in creating the Frailty Index's used

and also in drafting the chapter. I conducted and interpreted the analysis and wrote the chapter.

Chapter 8: I conceived the idea for this study. I conducted and interpreted the analysis and wrote the chapter. Dr Ruth Keir contributed substantially to retrospective NIHSS assessment for this study.

Chapter 9: I wrote the chapter.

Publications and Conferences

Publications related to thesis

Taylor-Rowan M, Momoh O, Ayerbe L, Evans JJ, Stott DJ, Quinn TJ (2018). Prevalence of pre-stroke depression and its association with post-stroke depression: a systematic review and meta-analysis. *Psychological Medicine* 1-12. <https://doi.org/10.1017/S0033291718002003>

Quinn TJ, Taylor-Rowan M, Coyte A, Clark AB, Musgrave SD, Metcalf AK, Day DJ, Bachmann MO, Warburton EA, Potter JF and Myint PK (2017) Pre-Stroke Modified Rankin Scale: Evaluation of Validity, Prognostic Accuracy, and Association with Treatment. *Front. Neurol.* 8:275. doi: 10.3389/fneur.2017.00275

Taylor-Rowan, M., Cuthbertson, G., Keir, R., Shaw, R., Drozdowska, B., Elliott, E., Stott, D. J. and Quinn, T. (2019) The prevalence of frailty amongst acute stroke patients, and evaluation of method of assessment. *Clinical Rehabilitation*. <https://doi.org/10.1177/0269215519841417>

Taylor-Rowan M, Keir R, Cuthbertson G, Shaw R, Drozdowska B, Elliott E, Evans J, Stott D, Quinn TJ. Pre-stroke frailty is independently associated with post-stroke cognition: a cross-sectional study. *J Int Neuropsychol Soc.* 2019 Mar 1:1-6. doi: 10.1017/S1355617719000092

Publications not included in thesis

Maclsaac RL, Ali M, Taylor-Rowan M, Rodgers H, Lees KR, Quinn TJ; VISTA Collaborators. Use of a 3-Item Short-Form Version of the Barthel Index for Use in Stroke: Systematic Review and External Validation. *Stroke.* 2017 Mar;48(3):618-623. doi: 10.1161/STROKEAHA.116.014789.

Taylor-Rowan M, Wilson A, Dawson J and Quinn TJ (2018) Functional Assessment for Acute Stroke Trials: Properties, Analysis, and Application. *Front. Neurol.* 9:191. doi: 10.3389/fneur.2018.00191

Papers in peer review

Shaw R, Drozdowska B, Taylor-Rowan M, Elliott E, Cuthbertson G, Stott D, Quinn T. Delirium in acute stroke, occurrence and risk factors. Submitted to 'Stroke'.

Conference Oral presentations

"Assessing the psychometric properties of the his "think frailty" tool." Presented at the British Geriatric Society Conference March 2018.

"Pre-stroke frailty is independently associated with post-stroke cognition: a cross-sectional study." Presented at The International Neuropsychological Society Conference July 2018.

Conference Poster presentations

VAS Cog; Amsterdam 2016

UK Stroke Forum' conference; Liverpool 2016, 2017

Opsyris; Nottingham 2017

Glasgow Royal Infirmary research day; 2017, 2018, 2019

British Geriatric Society; Nottingham 2018

International Neuropsychological Society; Prague 2018

Definitions/Abbreviations

AD8: Ascertain Dementia 8 questions

AF: Atrial Fibrillation

AMT-10: Abbreviated Mental Test-10

ANOVA: Analysis of Variance

APPLE: Assessing Psychological Problems: a Longitudinal Evaluation

ASCNES: Anglia Stroke Clinical Network Evaluation Study

AUROC: Area Under Receiver Operating Characteristic

BDS: Blessed Dementia Scale

BP: systolic blood pressure

Cam-ICU: Confusion assessment method for the Intensive Care Unit

CASP: Critical Appraisal Skills Programme

CDR: Clinical Dementia Rating scale

CESD: Centre for Epidemiological Studies Depression scale

CIDI: Composite International Diagnostic Interview

CI: Confidence Interval

DSM: Diagnostic and Statistical Manual

GPcog: General Practitioner Assessment of Cognition

FI: Frailty Index

4AT: 4 A's Test

GC: Gillian Cuthbertson

GDS: Geriatric depression scale

GDS-SF: Geriatric depression scale short form

GRADE: The **Grading** of Recommendations Assessment, Development and Evaluation

GSRD: Glasgow Stroke Research Database

IQ: Intelligence Quotient

IQCODE: The Informant Questionnaire of Cognitive Decline in Elderly

IQCODE-SF: The Informant Questionnaire of Cognitive Decline in Elderly- Short Form

IQR: Interquartile range

LACS: Lacunar stroke

LOS: Length of Stay

MCI: Mild Cognitive Impairment

MDD: Major Depressive Disorder

MEWS: modified early warning score

Mini-MoCA: mini-Montreal Cognitive Assessment

MMSE: Mini-Mental State Examination

MOOSE: Meta-analysis Of Observational Studies in Epidemiology

MT: Martin Taylor-Rowan

mRS: modified Rankin Scale

NHS: National Health Service

NIHSS: National Institutes of Health Stroke Scale

OCS: Oxford Cognitive Screen

OCSP: Oxford Community Stroke Project

OM: Oyiza Momoh

OR: Odds Ratio

PACS: Partial anterior circulation stroke

PFP: Physical Frailty Phenotype

POCS: Posterior circulation stroke

PSD: Post-stroke depression

RoB: Risk of bias

ROC: Receiver Operating Characteristic

SADQ: Stroke Aphasic Depression Questionnaire

SADQ-H10: Stroke Aphasic Depression Questionnaire
Hospital version

SCID: Structured Clinical Interview for Depression

SD: Standard Deviation

STARDem: Standards for Reporting of Diagnostic Accuracy studies in Dementia

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

SOIP: speed of information processing

SU: stroke unit

TACS: Total anterior circulation stroke

TIA: transient ischaemic attack

TQ: Terence Quinn

VIF: Variance inflation factors

WHO: World Health Organisation

1. What do we know about the psychological impact of a stroke?

1.1 What is cognition and what is depression?

Before beginning the discussion of the psychological impact of stroke, it is important to define what specifically is being referred to by the terms 'cognition' and 'depression'.

Cognition is the mental process of acquiring knowledge and understanding through thought, experience and senses. It includes the domains of memory, language, attention, executive functioning and visuospatial processing. Cognitive impairment is the disruption of functioning of any one of these domains. The most severe form of cognitive impairment is that of dementia. Dementia is an umbrella term that encapsulates a range of neurodegenerative disorders (e.g. Alzheimer's disease; Vascular dementia; Lewy body dementia; Frontotemporal dementia), which are chronic, progressive and cause multi-domain cognitive impairment. Dementia is not specifically classified by the Diagnostic and Statistical Manual (DSM) version IV (28) but can be inferred as consisting of memory impairment, plus one or more of aphasia, apraxia, agnosia, and executive dysfunction. Moreover, these cognitive deficits must impair daily functioning and represent a significant decline from previous levels of functioning; however, they must also not be better explained by disorders such as major depressive disorder (MDD) or schizophrenia, nor be attributable to an acute fluctuating disorder, such as delirium. (29) Fundamentally, dementia differs from non-dementia cognitive impairment in that it implies a continued, progressive deterioration in cognition that substantially disrupts daily functioning and will ultimately result in death.

Depression, meanwhile, is a disorder of mood. The most severe form of depression is major depressive disorder, which is diagnosed, according to the DSM-5 (30) if someone experiences feeling sad and/or a loss of interest or pleasure in everyday activities, plus 3-4 additional symptoms during the same 2-week period. Additional symptoms include reduced/increased appetite,

reduced/increased sleep, severe fatigue, feelings of worthlessness or guilt, feeling agitated/slowed down, diminished ability to concentrate/make everyday decisions, and recurrent thoughts of death/suicidal ideation. For MDD to be diagnosed, the presence of such symptoms must also cause clinically significant distress or impact daily functioning, such as ability to perform at work or interactions with peers. Milder forms of depression (such as minor depressive disorder) can also be diagnosed in which only 2-4 of the aforementioned symptoms are present, provided one of them is feelings of sadness or loss of interest/pleasure in everyday activities; and longer-term or season-specific depressions such as persistent depressive disorder or seasonal affective disorder reflect the presence of the aforementioned symptoms over prolonged periods of time (often months or years).

In addition to the traditionally recognised depressive disorders, vascular forms of depression may exist. Although not acknowledged by the DSM, vascular depression is thought to be organic in nature, occurring as a consequence of vascular damage to the frontal-subcortical regions of the brain.(31) Its symptoms largely overlap with MDD, and while low mood or anhedonia must be present, it is more prominently characterised by issues with psychomotor slowing, apathy, and cognitive impairment (particularly impaired executive functioning and reduced processing speed) than is typically seen in MDD.(32)

1.2 Current understanding of the natural history of psychological impact of stroke

Considerable research has taken place in recent years designed to develop our understanding of post-stroke psychological effects. Typically, research into the impact of stroke on cognition and mood has attempted to establish prevalence, risk factors, post-stroke trajectories of recovery or further decline, and specific cognitive domains affected following stroke.

This section will outline our current understanding of each of these areas in relation to post-stroke cognition and depression.

1.2.1 Cognition and dementia

1.2.1.1 Prevalence

Current evidence suggests that the majority of stroke patients experience impairment or decline in cognition.(33) Linden et al., (2004)(34) report cognitive impairment can be identified in around 61% of patients 20 months after stroke. This is two-times higher than the rate (31%) they observed in an age-matched control population. However, reported prevalence rates in this field have been highly heterogeneous. Patel et al., (2003)(35) reported that rates of vascular cognitive impairment varied from 15-39% based on clinical setting and time-frame assessed (3 months-3 years); while Pohjasvaara et al., (1997)(36) found further variation dependent upon age group, with rates varying from 45.7% in 55-65-year olds, up to 74.1% for 75-85 year olds.

In similar vein, post-stroke dementia prevalence rates range from 7.4% to 41.3% across studies.(37) Rates of dementia found in stroke are typically higher in hospital settings (20.3%-26.5%) than in population settings (7.4%). Post-stroke dementia in first-ever stroke survivors is reported as 10%; while 33% of recurrent stroke survivors develop post-stroke dementia. (37) By comparison, dementia prevalence is reportedly 7% in the general older adult population. (38)

Efforts to establish prevalence of dementia or cognitive impairment in stroke and determine how these rates compare against those of the general older-adult population are often confounded by varying definitions applied between studies.(28, 39) However, the general trend is that dementia presents an even greater burden in the stroke population than it does in the older-adult population.

1.2.1.2 Risk factors

A number of demographic and clinical risk factors have been associated with increasing risk of post-stroke cognitive impairment and dementia.

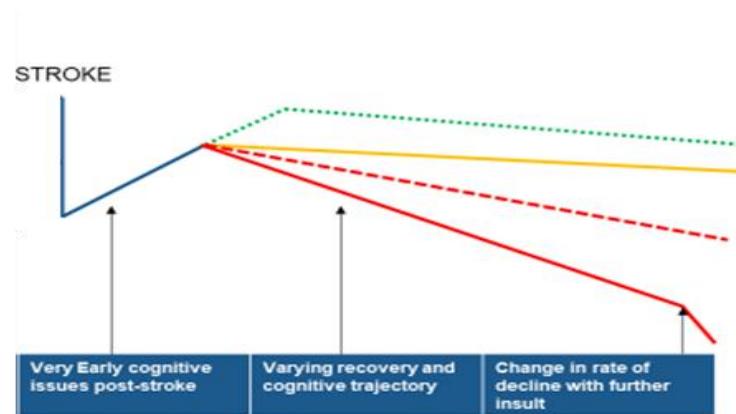
Demographic risk factors include increasing age and low levels of education. (40-42) Cited clinical risk factors are numerous, but inconsistent. Atrial fibrillation, (40) hypertension, (43) myocardial infarction (44) and diabetes (45) have all been associated with increased risk of cognitive impairment and dementia in stroke populations. However, Elkins et al., (2004)(46) point out that any proposed risk association may not be attributable to a single risk factor; rather, increased risk may be the product of the number and combination of risk factors that are present. Moreover, any risk may in fact be indirect; for instance, some risk factors may increase risk of stroke (re)occurrence, which in turn increases risk of cognitive impairment or dementia. (33)

Stroke-related factors are regarded as the greatest determinants of post-stroke dementia. (37, 47) Stroke severity, stroke recurrence, and stroke location have all been implicated in onset of post-stroke dementia. (37) Investigations have also taken place into the influence of stroke-type. (48) Cerebral strokes appear to affect cognition more than brainstem strokes.(37) Lacunar strokes that affect the deep lying subcortical regions of the brain, however, appear just as disruptive to cognition as cerebral strokes. (49) This may be related to lacunar strokes' position on the spectrum of small vessel disease, which itself is associated with cognitive impairment via diffuse structural damage. (49)

1.2.1.3 Trajectories

Continued cognitive decline is common post-stroke; the cumulative dementia incidence rate is reported to be 3% per annum, when recurrent strokes are factored in. (37) However, there is evidence that the trajectories of impairment are variable. (see Figure 1-1)

Figure 1-1. Trajectories of cognitive impairment after stroke



Likelihood and extent of deterioration can be influenced by existent risk factors such as older age, lower education and recurrent stroke. (50-52) Importantly however, not all post-stroke cognition follows a descending trajectory and there is evidence of recovery. For instance, Desmond et al., (1996)(53) found that 19/151 patients experienced recovery of cognitive function, and this improvement was apparent for most within the first 3 months. Similarly, Del ser et al., (2005)(51) found that 7.8% of patients experienced improvement in cognitive status at 24 months, while Rasquin et al., (2005)(50) reported that 20% of patients with post-stroke mild cognitive impairment (MCI) at 1 month demonstrated normal cognitive function at later assessment.

1.2.1.4 Domains affected

Strategic lesions can theoretically induce cognitive impairment of any kind, and global cognitive impairment is common post-stroke; however, the most frequently affected cognitive domains in stroke patients appear to be speed of information processing (SOIP) and attention. (54) This is particularly the case early after stroke (i.e. first month), in which as many as 70% of stroke patients reportedly experience impairments in SOIP and attention. (55) By contrast, visual and verbal memory may be the least affected domains following stroke, with impairments reportedly occurring in around 15% and 30% of stroke patients, respectively. (55) Albeit, some studies have found memory impairments existent in up to 60% if stroke patients, 3 months following stroke. (56)

Interestingly, trajectories of recovery seem to vary by domain. Hurford et al., (2013)(55) found that the most prominent early impairments also demonstrated the greatest recovery potential. Specifically, impairments in attention and SOIP declined from 70% in the acute period to <40% at 3 months. The least affected cognitive domains—visual and verbal memory— meanwhile, demonstrated the lowest recovery potential, with no statistically significant change in prevalence taking place between the acute period and 3 months. This may suggest that, in many cases, existent memory impairments following stroke reflects underlying neurodegeneration that pre-dates the stroke. (55) However, research on domain-specific recovery potential has been inconsistent. Lesniak et al., (2008)(57) found that recovery was greatest in the domains of executive functioning, aphasia and long-term memory; whereas deficits in attention and short-term memory tended to persist. In contrast, Snaphaan and De Leeuw (2007)(58) found that prevalence of memory impairment declined from 23-55% at 3 months to 11-31% at 1 year. Therefore, no firm conclusion can be drawn at present as to underlying nature of any given form of post-stroke cognitive impairment.

1.2.2 Depression

1.2.2.1 Prevalence

Depression following stroke appears to be highly prevalent and rates are reportedly several times that of the general older adult population; (59, 60) albeit, similar to post-stroke cognition, the specific rates are often heterogeneous across studies. This variability is typically attributed to variations in assessment type, study setting, follow-up time from stroke, and study setting. (61)

The most frequently reported pooled prevalence of depression after stroke is ~30%. (59, 62) However, Ayerbe et al., (2013)(63) report more than 50% of stroke patients are expected to experience post-stroke depressive symptoms, if not necessarily clinical depression. When restricted to cases of major depression only, rates of post-stroke depression are suggested to be around 17%. (64)

Alteration of prevalence over time is an area of active debate. Some (65) suggest that most cases of depression following stroke occur inside the first year, with prevalence deteriorating over time; whereas others suggest a stable prevalence rate of ~30% up to 10 years post-stroke. (63)

1.2.2.2 Risk factors

A large variety of variables have been investigated as potential risk factors for depression after stroke. Attempts have been made by several systematic reviews to pinpoint the most important risk factors; however, their conclusions are often conflicting. (59, 62, 64, 66-69)

Sociodemographic risk factors including age, sex, lifestyle and lack of social support have been related to onset of post-stroke depression. (70, 71)

Psychological factors such as cognitive impairment, anxiety, personality type, subjective experience of stroke, and patient coping strategies have all been associated with post-stroke depression, along with functional risk factors like post-stroke disability and level of independence. (59, 66)

Demonstrated associations between many of the aforementioned variables and post-stroke depression onset have been argued to indicate that depression after stroke is largely a product of the experience and psychological consequences of the stroke. (59) However, others champion an organic aetiology to post-stroke depression. (62)

The organic theories of post-stroke depression posit that depression may be induced as a direct consequence of biological damage provoked by brain injury. In support of this, stroke lesion size and lesion location have been implicated in development of post-stroke depression, the latter particularly in the first 2 months following stroke. (64, 72) Specifically, left-sided strokes that produce lesions in the frontal lobe and basal ganglia have been linked to development of post-stroke depression; and severity of depressive symptoms have been linked to lesion proximity from the left frontal pole. (72) However, most subsequent studies have failed to replicate the observed association between stroke lesion location and post-stroke depression (73) and some have even found associations

between depression and lesions in the contralateral hemisphere. (74) Reasons for these contrasting results have been attributed to the way in which depression is assessed across studies, as well as variability in study setting, neuroimaging methods applied, exclusion of aphasic patients, and definition of lesion location. (72, 73) Perhaps less controversially, extent of subcortical vascular damage (and subcortical small vessel disease) has also been associated with onset of post-stroke depression. (31) It is argued that post-stroke depression may be induced via vascular damage that causes interference to subcortical frontal lobe circuits and monoaminergic and serotonergic pathways, disrupting the emotional circuits of the brain.

1.2.2.3 Trajectories

Current research describes substantial recovery potential from depression after stroke. Specific rates are uncertain however, with reported recovery at 1 year, following a depressive episode in the first 3 months post-stroke, ranging from 15%-57%. (63)

Although a relatively quick recovery from a first instance of post-stroke depression is common for many patients, recurrence appears highly likely and can occur even after a long period of remission. (63) Ayerbe et al., (2013)(63) report that 38% of stroke patients experience a recurrent bout of depressive symptoms at 2 years; and most patients appear to experience recurrence of depressive symptoms generally, some of which reoccur as long as 15 years after the stroke event.

Recovery potential may however vary depending upon the nature of the depression; depressive disorders thought to be induced by vascular damage are proposed to demonstrate a more chronic nature and greater frequency of recurrence. (75)

1.2.3 Summary and conclusions

Overall, research to date suggests that psychological issues in stroke are substantial. While our specific understanding of the aetiology and natural

history of post-stroke cognitive impairment and depression is limited due to heterogeneous findings, the evidence broadly suggests that a majority of patients will experience psychological issues. Investigations into risk factors for post-stroke psychological problems have been extensive and it is clear that factors beyond the stroke itself are relevant. However, there is currently limited agreement as to the most pertinent risk factors for both post-stroke cognition and mood impairment. Finally, the evidence suggests that trajectories of cognitive impairment and depression following stroke are not straightforward. In general, it seems that while recovery is possible for both conditions, deterioration in cognition is common although can vary depending on the domain affected, while recurrence of depression likely.

Chapter 2. The pre-stroke state

As evidenced in chapter 1, psychological problems in stroke are substantial and there is much scope to improve our understanding of these issues. There are numerous areas of study that would help develop our comprehension of psychological problems in stroke. A very relevant, but to date particularly overlooked area is the pre-stroke state. Much of the current stroke-psychology literature is overly limited, frequently focusing upon post-stroke variables' contribution to psychological disorders, with little attention given to the influence of pre-stroke factors. Consequently, the contribution of the pre-stroke state to post-stroke psychology is less well understood. Improving our understanding of the pre-stroke state could broaden our perspective of the psychological problems that stroke patients experience, including aetiology and natural history. Both psychological and physical pre-stroke conditions are important to consider in this regard. This chapter will outline what we know regarding several pre-stroke variables and their relevance to the post-stroke psychological state. Specifically, the chapter will discuss risk associations, prevalence, and means of assessment of four pre-stroke conditions (cognitive impairment, depression, functional impairment/disability and frailty), as well as highlighting limitations regarding our understanding of these areas. Addressing these limitations will be the focus of subsequent chapters of this thesis.

2.1 Pre-stroke cognitive impairment and dementia

2.1.1 Risk association and Prevalence

While the stroke itself appears to be the major determinant of post-stroke dementia (37), presence of pre-stroke cognitive impairment has been regularly associated with increasing risk of post-stroke cognitive impairment and dementia.(37, 47) The prevalence of *any* pre-stroke cognitive impairment (e.g. MCI plus dementia prevalence combined) is not well described; however, a systematic review of the literature (37) suggests the prevalence of pre-stroke *dementia* lies between 9-14%, depending on setting. This may even be an underestimation as many of the studies on which these rates are based employ

retrospective methods to determine dementia prevalence. (37) There are a number of issues with this assessment approach that may hinder our understanding of pre-stroke cognition and, consequently, our wider understanding of psychological issues in stroke. The specific issues with current pre-stroke cognition assessment are outlined in detail in section 2.1.2.

2.1.2. Methods of assessing pre-stroke cognitive impairment and dementia

Pre-stroke cognition can be assessed objectively via neuropsychological tests, provided they are conducted before the stroke occurrence. This is the optimal approach; however, it is difficult to establish pre-stroke cognition in this way as neuropsychological assessments are not routinely conducted within the general population; hence, the pre-stroke cognitive state is typically assessed subjectively via a retrospective interview or questionnaire.

When patients are cognitively impaired, their ability to provide insight into their own cognitive issues as well as any deterioration over time is often lacking; therefore, reports from ‘informants’ (third parties that knows the patients well) are preferred over patient self-reports. As such, completing a retrospective interview/questionnaire with an informant is a favourable method employed to establish pre-stroke cognition.

There are many informant tools that might be used for assessment of pre-stroke cognition. (see Figure 2-1) The Informant Questionnaire of Cognitive Decline in Elderly (IQCODE); the Ascertain Dementia 8 questions (AD8); the General Practitioner Assessment of Cognition (GPCog); and the Blessed Dementia Scale (BDS) are typical examples. However, these tools were designed to establish ‘present day’ cognition, not retrospective cognition that predates a particular medical event; moreover, there are potential stroke-specific issues with the use of such tools when employed to assess premorbid cognition. This section will outline some of the key issues concerning the retrospective informant approach for assessment of pre-stroke cognition by detailing the evidence regarding the psychometric properties of informant-based tools.

The IQCODE is the most commonly employed tool in stroke. (76) Historically, the IQCODE was designed to detect cognitive decline in community dwelling older adult populations. (77) It is a 32-item questionnaire that asks an informant questions concerning how their friend/relative's cognition has changed over the past 10 years. It operates on a 5-point ordinal scale and generates a score ranging from 1 (much improved) to 5 (much worse); scores closer to 5 suggest greater cognitive impairment.

As it is the most commonly employed tool, I will use our current understanding of the IQCODE's psychometric properties and application as an exemplar of the status of pre-stroke cognition assessment and the wider issues of this area.

Figure 2-1. Common Informant tools for assessing cognition

Informant Questionnaire Cognitive Decline in the Elderly (IQCODE)
Ascertain Dementia 8 questions (AD8)
Deterioration Cognitive Observee (DECO)
Blessed Dementia Scale (BDS)
General Practitioner assessment of Cognition (GPCog)
Concordant Informant Dementia Scale (CIDS)
Symptoms of Dementia Screener (SDS)
Short Memory Questionnaire (SMQ)
Brief Cognitive Scale (BCS)
Dementia Questionnaire (DQ)

2.1.2.1 Psychometric properties of the IQCODE

A number of key variables are deemed important for the operational use of a measurement tool according to the theory of psychometrics (78): validity, reliability, acceptability, feasibility and responsiveness. (see Table 2-1) Extensive work has been conducted on the psychometric properties of the IQCODE. Research to date highlights uncertainty regarding 3 of the aforementioned properties.

Table 2-1. Description of the core psychometric properties

PSYCHOMETRIC PROPERTY	
<i>Validity</i>	The degree to which a tool measures what it purports to measure.
Concurrent validity	The extent to which a tool's results correspond to other. measures associated with the outcome of interests (i.e., functional disability).
Construct validity	A tool's association with other tools that measure the same, or a similar construct.
Predictive validity	Ability of the tool to predict future events.
<i>Reliability</i>	Refers to a tool's consistency in scoring over multiple assessments.
Inter-rater reliability	Consistency of scoring across different assessors.
Intra-rater reliability	Consistency of scoring within the same assessor.
<i>Acceptability</i>	The acceptability is the willingness of the participant to undergo/take part in the assessment.
<i>Feasibility</i>	The practicality or reasonableness with which a tool can be used. Can incorporate measures of acceptability to rater and patient.
<i>Responsiveness</i>	The ability of the scale to detect change after repeated testing (either improvement or further decline).

Validity:

Validation work has compared the IQCODE against measures of cognitive change, neuropathology, neuroimaging and neuropsychological assessment and shown significant, moderate correlations with each; (79) factor analysis suggests the tool is a measure of general cognitive decline. (79) In acute care settings, sensitivity and specificity for detection of dementia, based on meta-analysis, (77) is reported to be 91% and 66%, respectively (at a cut-point of 3.3 or closest). The overall reported diagnostic test accuracy evidence is comparable to that of direct-to-patient, objective cognitive assessments such as the Mini-Mental State Examination (MMSE);(80) and there is even evidence that the tool is less susceptible to influences of education and cultural norms than objective cognitive assessments. (79)

However, IQCODE validation studies are often limited by the incorporation of the IQCODE score into the gold standard reference assessment to which it is compared during diagnostic test accuracy evaluation. This lack of blinding and cross contamination is a major source of bias regarding the IQCODE's reported diagnostic properties, typically resulting in overestimation of the tool's accuracy. (81) In addition, population restrictions are frequent in IQCODE diagnostic test accuracy studies, which limits the generalisability of the reported rates. Furthermore, evidence related to the IQCODE's ability to detect non-dementia level cognitive impairment is sparse and inconsistent (82-85), and there are indications that other informant tools (e.g. AD8) may outperform the IQCODE in the context of diagnosing non-dementia level cognitive impairment. (82)

Added to these general issues regarding the contemporary evidence of the IQCODE's validity are matters that pertain more specifically to stroke. For instance, McGovern et al., (2016) found that there are no validation studies investigating use of the IQCODE (or any informant tool) as a means of assessing pre-stroke cognition, despite its widespread use for this purpose. This is concerning since it is not uncommon for tools to perform differently across medical populations. (86) Indeed, stroke populations often demonstrate a greater prevalence of specific conditions that can influence the tool's diagnostic test accuracy, than are found in the general geriatric population.

To elaborate, vascular problems (e.g. small vessel disease, previous-stroke) are common in stroke populations (87) and are believed to primarily impair the cognitive domains ‘executive functioning’, ‘speed of information processing’, and ‘attention’. (76) Yet, the IQCODE has a memory-based focus to its items. Thus, there is greater potential for individuals with predominantly non-memory-related cognitive problems to go unrecognised, reducing the sensitivity of the tool.

The IQCODE describes change in performance on various functional tasks as a means of determining presence of cognitive impairment. Depression can also influence many of the functional tasks described; (79) and, as depression is a risk factor for stroke, (88) pre-stroke depression may be more common in stroke populations than in non-stroke populations. Similarly, certain functional tasks may not be performed as well as before due to onset of physical disabilities (e.g. learning how to use a new gadget or machine around the house; handling money for shopping; handling financial matters), which again may be more common in stroke than in non-stroke populations. (89) These latter two conditions may consequently impact upon the specificity of the tool when applied to a stroke population.

Acceptability and Feasibility:

Investigations as to the acceptability and feasibility of the tool also highlight difficulties. The IQCODE was designed for use in a community dwelling population where informants are at hand and assessors have time to address queries. In a busy, secondary acute care setting however, suitable informants may not be as readily available, and staff may not have the time to supervise completion/answer queries, potentially adversely affecting the tool’s validity. While small scale studies with dedicated research assistants can achieve informant tool completion rates of around 80% (90), McGovern et al., (2016)(76) report a typically high non-completion rate of the IQCODE when used in stroke research, and Smeeth et al.,(2001)(91) report that postal forms of the questionnaire are associated with missing data.

This propensity for non-completion suggests that either the acceptability or feasibility of the questionnaire may be limited. The reasons for this are unclear. While direct cognitive assessments often demonstrate poor acceptability due to issues such as distress arising from deficient performance, or the high mental demand required for completion, informant questionnaires do not obviously entail such issues. It may be that informants feel the questions are not relevant to their relative or are too vague to be answered acceptably. There are currently no qualitative analyses of people's experience with these questionnaires to enlighten in this area. On this basis, recent reviews (77) have called for more work to establish how feasible informant tools are in secondary care settings.

Heterogeneity of use and optimal tool selection:

On a final note, a major limitation of the IQCODE is that there is little guidance as to why it should be selected over any of a number of informant tools. There are a vast range of informant tools for cognitive assessment available, and the extent of choice can be reflected in heterogeneous operationalisation of cognitive assessment tools in practice. (92) To date, there have been no direct comparisons of informant tools that determine the suitability of their use in stroke. As such, tool selection is often arbitrary, which contributes largely avoidable heterogeneity to the field. Added to this, employment of such informant tools frequently demonstrates inconsistency of application. (92) Variable cut-off points for dementia diagnosis are employed for the IQCODE (e.g. 3.3-4.1). (77) Cut-off points define the properties of the tool in relation to sensitivity and specificity. Reducing a cut-off point to improve sensitivity may increase identification of patients with cognitive impairment; however, resultant specificity will inevitably suffer. This heightens misidentification risk of cognitively unimpaired individuals as demented. Heterogeneity of application is therefore another pernicious issue regarding the current utilisation of the IQCODE as a means of assessing pre-stroke cognition and could unnecessarily induce misdiagnosis clinically as well as further exacerbate inconsistency in stroke-cognition research.

2.1.3 Summary and conclusion

Despite its obvious relevance to understanding post-stroke cognitive impairment, a robust and extensive understanding of pre-stroke cognitive impairment is lacking. This is in part related to issues regarding assessment. Informant tools have inherent limitations of various psychometric properties, but the extent of these limitations are particularly poorly understood within a stroke context. While necessities of pragmatism dictate that a limited retrospective approach to pre-stroke cognition assessment must typically be applied, issues with psychometric properties are exacerbated by variability of tool selection and application. Arguably, this stems from a lack of any explicit guidance as to appropriate tool selection and utilisation as no studies have yet validated and compared competing informant tools within the same study or established optimal cut-off points. Overall, the issues with pre-stroke assessment confound our general understanding of pre-stroke cognition. Such problems may however be partially alleviated by generating a greater understanding of how well cognition assessment tools operate within stroke (both independently and in relation to competing tools), thus providing guidance for optimal pre-stroke cognitive assessment and reducing unnecessary heterogeneity. This will be the focus of chapter 3.

2.2 Pre-stroke depression

2.2.1. Risk association and Prevalence

Our understanding of pre-stroke depression is fundamentally limited in general terms. The vast majority of research in the context of pre-stroke depression and its relation to post-stroke psychological conditions is in reference to a posited risk association with post-stroke depression. (59, 66-68) While pre-stroke depression is frequently cited, and treated clinically, as a risk factor for post-stroke depression, the evidence base for the association is inconsistent. A number of studies have failed to find an association (93-96) and systematic reviews that conclude in favour of an association cite evidence that falls short of overwhelming (e.g. Kutlubaev et al., (2014)(66) state 5/8 studies found a

significant association between pre-stroke depression and presence of post-stroke depression). Little investigation has been conducted into the reasons why some studies find an association where others fail, and there are those who doubt that pre-stroke depression is a meaningful risk factor for post-stroke depression. (95) Inadequate regression-model power and differences in covariate control or assessment method may be contributing factors to the inconsistency, but this requires to be formally investigated.

Similarly, the prevalence of pre-stroke depression is not well described. Only 1 study to date has explicitly investigated the prevalence of pre-stroke depression. Reid et al., (2010)(97) report 10% of stroke patients are depressed within the preceding 6 months of the stroke. However, a large range (e.g. <1%-52%) of pre-stroke depression prevalence rates are reported across studies that investigate post-stroke depression. (98, 99) This stark variability in reported rates may in part reflect differing assessment methods employed. Indeed, when utilising the same patient cohort, but adopting differing pre-stroke depression assessment methods, McCarthy et al., (2016)(100) and Wulsin et al., (2001)(98) reported considerably differing rates (13% vs 52%).

The lack of an established pre-stroke depression prevalence rate is a missing component in our overall ability to comprehend the natural history of post-stroke depression. Furthermore, prevalence of pre-stroke depression may provide insight regarding the predominant cause of most cases of post-stroke depression, as well as the reasons why post-stroke depression is so common (e.g. is the prevalence of depression after stroke so high because this population are also extremely prone to depression before their stroke?). As such, this is an area that needs addressed.

2.2.2. Methods of Assessing pre-stroke depression

The specific methods employed for assessment of pre-stroke depression have not been thoroughly investigated. Depression assessment tools, such as the Centre for Epidemiological Studies Depression scale (CESD), Composite International Diagnostic Interview (CIDI), Structured Clinical Interview for Depression (SCID), and medical records can all be employed. However, at present, we have limited

insight into what the favoured or optimal approach is, or the psychometric properties of the methods employed. As discussed in section 2.1, inadequate guidance in choice and use of assessment typically leads to heterogeneity; and clinicians report that lack of knowledge and consensus of the best measures are barriers to adopting routine depression screening. (101) This lack of clarity is therefore a major gap in the pre-stroke depression literature and could ultimately interfere with adoption of future implementation of pre-stroke depression screening, should this be identified as beneficial. Research into pre-stroke depression assessment methods is therefore warranted.

2.2.3 Summary and conclusion

Pre-stroke depression is a poorly described condition. There are several fundamental points that are unestablished: 1) There appears to be a risk association with presence of post-stroke depression; however, detractors remain and clarification on this point is required. 2) The prevalence of the condition is unclear, and the range of reported rates is vast. 3) Both the typical and optimal means of assessing pre-stroke depression, along with their respective psychometric properties, have not been well described.

An investigation of prevalence, risk association and assessment methods for pre-stroke depression is therefore required in order to establish fundamental information in this area. This will be the focus of chapters 4 and 5.

2.3 Pre-stroke functional impairment/disability

2.3.1 Prevalence and risk association

Pre-stroke function is well recognised for its relevance to understanding post-stroke functional outcomes and suitability for treatment. It is already frequently assessed as part of a suitability assessment for aggressive post-stroke treatments, such as thrombolysis and thrombectomy and in gauging suitability

for stroke trials. (102, 103) In the context of psychology in stroke, the relevance of patient functioning becomes apparent when we consider that a diagnosis of dementia (pre or post-stroke) requires identification of functional impairment in addition to cognitive impairment.

Pre-stroke functional impairment has been identified as a risk factor for post-stroke dementia (37) and is reportedly present in 25-54% of stroke patients. (89, 104) However, there have been a lack of systematic reviews on this topic and, similar to pre-stroke depression, there is limited research looking into the epidemiology of pre-stroke functional impairment in general. Much of the research to date is based upon measuring pre-stroke function via the pre-stroke modified Rankin Scale (mRS), which, as is discussed in detail in section 2.3.2, may not be suited for this purpose. It is therefore unclear how reliable these reported prevalence rates and risk associations are. There is a need for more work in relation to fundamental epidemiological information with regards to pre-stroke functional impairment.

2.3.2 Methods of assessing pre-stroke function/disability

The most commonly used functional assessment measure in stroke is the modified Rankin Scale. The mRS adopts a 7-point hierarchical ordinal scale to measure functional independence. It was historically designed to assess post-stroke outcomes for local audit purposes and initially employed to aid descriptive analysis of the natural history of stroke and its putative treatments. (105) It was never intended for use in research, or as a measure of pre-stroke functioning; yet it has frequently been employed in this way. (89)

Despite its common use as a measure of pre-stroke disability, there has been very little clinometric or validation work regarding pre-stroke functional assessment. This is problematic as the wording of the various levels of the scale, and the criteria used to distinguish one mRS grade from another, assume a previous stroke. Although there is guidance on pre-stroke mRS scoring in those with a previous stroke event (106, 107) there is no internationally accepted, consensus on how to use mRS as a pre-stroke measure in patients who have

never had a previous stroke. (106, 108) This can cause issues in application when the scale is used to measure function before a stroke event.

Work on the psychometric properties of the pre-stroke mRS to date are not overly encouraging. Fearon et al., (2012)(89) reported that the tool has only moderate interobserver reliability—albeit this is similar to observed reliability when the mRS is used to measure post-stroke functioning. Predictive validity is demonstrated via associations with mortality and length of hospital stay (109)—though the extent to which this is driven by a differing process of care is unclear. Concurrent validity is reportedly moderate, according to correlations with markers of comorbidity;(89) however, there are also concerning discrepancies between pre-stroke mRS scores and proportions living independently at home. (89) Moreover, this latter validation work (89) was based on a relatively small sample size, and some (106) argue that the pre-stroke mRS is not fit for purpose as a measure of pre-stroke functional assessment. Further validation work controlling for differences in post-stroke care-pathway, in a larger, more generalisable population, is therefore required to better establish the mRS' suitability in pre-stroke functional assessment.

2.3.3 Summary and conclusions

Pre-stroke function is another area in which fundamental epidemiological information is generally lacking. It has been associated with post-stroke dementia and available prevalence rates suggest it is present in one-quarter to one half of stroke patients. Its relevance to dementia diagnosis as well as more general health outcomes and suitability for treatment is well recognised and it is already routinely assessed on this basis. However, despite not being designed for assessment of pre-stroke function, the mRS is the predominant measure employed and it has not been well validated when used in a pre-stroke context. While establishing fundamental epidemiological information is important, there is a pressing need to evaluate the validity of the pre-stroke mRS, not just for our understanding of psychological issues in stroke, but for general healthcare use and research as well. Validating the pre-stroke mRS will therefore be the focus of chapter 6.

2.4 Pre-stroke frailty

Frailty is a condition of emerging interest in clinical practice and research generally. There is currently no accepted operational definition of frailty; however, the two predominant positions are the Fried ‘frailty phenotype’ (110) and the Rockwood ‘accumulated deficits’ concepts of frailty. (111) The Fried perspective views frailty as a unidimensional biological syndrome, characterised by physical symptoms including weight loss, exhaustion, slow mobility, limited physical activity and weakness. The Rockwood perspective views frailty as a multidimensional construct and state of heightened risk; a by-product of the accumulation of age-related health conditions, culminating in a reduced physiological reserve. Regardless of the definition adopted, there is a general consensus that frailty is a state of multisystem impairment and reduced resistance to stressors that ultimately leads to increased vulnerability to poor outcomes. (112) In addition to a frail status, patients can be in a state of ‘prefrailty’, defined as a state of heightened risk for becoming frail but not currently considered frail.

2.4.1 Risk association and prevalence

The presence of frailty has been associated with increased risk for onset of delirium upon hospital admission along with risk of dementia. (113) Frailty prevalence within the older adult population is thought to be increasing and reported rates vary from 4-59% depending on population and definition. (114) In the context of stroke however, frailty is a largely overlooked concept. As such, specific prevalence rates and risk associations with post-stroke cognition are unestablished. Risk factors (e.g. hypertension, diabetes) for the onset of frailty overlap with those for stroke occurrence;(115) hence there is reason to suspect that the burden of frailty in stroke may be substantial.

Furthermore, the Rockwood group propose that the accumulation of age-related medical conditions may lead to a state of physiological exhaustion and impaired repair mechanisms, thus limiting the body and brain’s ability to respond to, and minimise the damage of, further stressors. (116) In this sense, it is possible that a heightened state of brain ‘vulnerability’ may induce more substantial cognitive

consequences for patients who are frail before the stroke than those experienced by non-frail patients. While a number of important risk factors for post-stroke cognitive impairment have already been established, the prospect of a risk association between pre-stroke frailty and post-stroke cognition is yet to be investigated.

Establishing the prevalence of frailty in stroke and investigating the possibility of a risk association with post-stroke cognition is therefore needed.

2.4.2. Methods of assessing pre-stroke frailty

Frailty assessment has become routine in general practitioner settings, (117) but has not yet been adopted routinely in stroke. Frailty assessment varies depending upon the operational definition adopted. In total, there are as many as 67 different frailty assessment tools available.(118) The most commonly used assessment tools are the Physical Frailty Phenotype (PFP) assessment method and the Rockwood Frailty Index (FI). (110, 119)

The PFP method measures 5 physical conditions (weakness, slow gait speed, exhaustion, involuntary weight loss, and sedentary behaviour), believed to be characteristic of frailty, via a series of tasks and questions. Weakness is assessed via grip strength on a dynamometer; slow gait speed is determined via duration to walk 15 feet; exhaustion via the question: “how often in the last week did you feel that everything was an effort or that you could not get going?”; involuntary weight loss via the question: “have you lost more the 4kg (or half a stone) unintentionally over the past year?”; and sedentary behaviour via the question: “what is your level of physical activity”. In the context of stroke, grip strength and walking speed may be challenging to measure in a busy acute setting or confounded by neurological issues. Self/informant report versions of the PFP assessment are available that alleviate the need for the physical components of this frailty measure. Adoption of self/informant-report measures may therefore be a more pragmatic means of measuring phenotypical frailty in stroke.

Validity of self-report PFP methods are comparable to those methods which incorporate the physical assessment and can actually outperform physical assessment of PFP assessment in both discriminative ability and predictive validity. (120) However, such validation methods have only taken place in non-stroke populations; hence it remains to be seen if the validity of such self-report tools translates to the stroke setting.

The FI applies the accumulated deficits concept of frailty and establishes frailty on a continuous scale ranging from 0-100, based upon the number of preselected, age-related health conditions an individual has acquired over the life-time. This assessment method has the advantage of using patient case-history to establish frailty and can conceivably be formulised for any patient. Detractors point out that the process of establishing frailty via patient medical records can be time consuming, such that it is not feasible for use in routine clinical practice. However, there is potential for an electronic Frailty Index that can be automatically generated for each patient upon admission and may help to overcome this limitation. (121)

The FI demonstrates good predictive validity, as long as a minimum of 30 conditions (meeting distinct requirements) are present.(122) Moreover, this predictive validity is maintained regardless of the conditions selected in the index. The number of, and selection of, conditions on a given index can vary, making this method of assessing frailty advantageous for utilisation given routinely collected clinical data. However, just like the PFP approach, this method of assessing frailty has not been validated for use in a stroke population.

There is a need therefore to validate predominant frailty assessment methods for use in the stroke population.

2.4.3. Summary and conclusion

Pre-stroke frailty is a largely overlooked concept in stroke: Fundamental questions related to prevalence and validity of assessment methods have not been answered. In addition, there is a potentially important relationship between pre-stroke frailty and post-stroke cognition that has not been

investigated. The prevalence of pre-stroke frailty, the validity of prominent assessment methods, and its risk association with post-stroke cognitive impairment will be explored in chapters 7 and 8.

2.5. Overall conclusions and specific aims of this thesis

Psychological consequences following stroke are common and undeniably important. However, while our understanding of the psychological impact of stroke is developing, we cannot generate a comprehensive and robust understanding without greater knowledge of the pre-stroke state. Fundamental questions related to prevalence and risk associations of both psychological and physical pre-stroke conditions remain to be answered. Accurate assessment of pre-stroke variables is a key component to the investigation of these areas. While assessment of the pre-stroke state often requires a limited retrospective approach, the basic issues with this method are amplified by lack of knowledge regarding optimal tool selection and use, contributing unnecessary heterogeneity to an already heterogeneous field. Methods employed for the assessment of the pre-stroke state need validation; and better guidance for appropriate selection and application is required: If we do not know how to measure pre-stroke variables effectively, we cannot deduce the extent to which this influences post-stroke psychology.

The aims for this thesis will therefore be:

- 1) To establish prevalence and risk associations of pre-stroke variables where they are lacking.
- 2) To validate prominent assessment tools used to assess the pre-stroke state in the domains of cognition, depression, disability and frailty.
- 3) To perform comparative analyses of tool performance so as to provide greater guidance as to the optimal tools available for assessment of pre-stroke conditions.

Chapter 3: Validation and comparison of informant questionnaires for assessment of pre-stroke cognitive impairment; a diagnostic test accuracy study.

3.1 Introduction

As discussed in chapter 2 section 2.1, the presence of pre-stroke cognitive impairment is relevant to post-stroke psychological dysfunction;(37) however, much of our understanding of pre-stroke cognition is based upon use of informant questionnaires that have not been validated for premorbid assessment in stroke.(76) Moreover, there is little guidance regarding optimal tool selection and use when informant tools are utilised in a pre-stroke context; this can be a source of unnecessary heterogeneity in the field and makes it difficult for clinicians to employ the best assessments for their practice.

The IQCODE is the most commonly used informant tool in stroke. (76) The IQCODE-SF is a 16-item version of the IQCODE. Recent reviews (77, 123) have demonstrated that the IQCODE-SF has similar diagnostic test accuracy to the 32-item version; hence the IQCODE-SF is often preferred in the acute stroke unit, where time for assessment is limited.

Alternative tools, such as the AD8, exist which have favourable properties over the IQCODE-SF. Specifically, the AD8 is shorter and easier to score than the IQCODE-SF. There is also evidence that it may be more sensitive to detecting both dementia and non-dementia level cognitive impairment—though the IQCODE-SF may be more specific. (77, 82, 83, 124) To date, the comparative diagnostic test accuracy of these tools has not been examined in stroke.

I therefore sought to validate and compare the diagnostic test accuracy of the IQCODE-SF and AD8 when used to detect pre-stroke cognitive impairment in an acute stroke population.

3.1.1 Hypotheses

My primary hypothesis was that both informant tools would be valid tools for assessing pre-stroke cognitive impairment; overall diagnostic test accuracy performance would be significantly above chance level.

My secondary hypothesis was that the pattern of sensitivity and specificity would vary between the tools.

3.2 Method

I followed STARDdem (Standards for Reporting of Diagnostic Accuracy studies in Dementia) guidelines for conduct and reporting in this study. (125)

3.2.1 Study design

This is sub-study of the ‘APPLE’ (Assessing Psychological Problems: a Longitudinal Evaluation) project. APPLE is a longitudinal study designed to assess cognition and mood over time in a stroke population. The protocol for APPLE can be seen in Appendix 1.

3.2.2 Setting

Patients admitted consecutively to the acute stroke unit of 7 participating hospitals across Scotland were approached to take part between 1st November 2016 and 1st December 2018. Participating hospitals were the Glasgow Royal Infirmary; Queen Elizabeth University Hospital; Queen Victoria Hospital (Fife); University Hospital Monklands; University Hospital Hairmyres; Aberdeen Royal Infirmary; Royal Alexandra Hospital. No restrictions were operated on age, time-frame since stroke, prior stroke, stroke-type, stroke-severity or comorbidity. All participating sites offered hyper-acute stroke services and admitted all patients with suspected stroke to specialist services.

3.2.3 Population

Participation required an eligible informant also willing to take part. Informants had to have known the patient for at least 10 years and see the patient on a regular basis (twice per week). Patients unable to consent to participation (e.g. due to severe aphasia or cognitive impairment) were still included if a proxy was willing to provide assent consent. Participants were however excluded if they were palliative, or if their informant was unable to speak fluent English. Participants were also excluded from analysis if their informant did not complete the informant questionnaires or if a gold standard diagnosis could not be derived.

3.2.4 Informant tool assessment

Each participant's informant was asked to complete the IQCODE-SF (16-item) and AD8, which were administered in alternating order from patient to patient by the on-site stroke research network nurses, trained in administration of the questionnaire.

The IQCODE-SF is a 16-item questionnaire that asks an informant questions regarding how their friend/relative's cognition has changed over the past 10 years. It operates on a 5-point ordinal scale and generates a score ranging from 1 (much improved) to 5 (much worse); scores closer to 5 suggest greater cognitive impairment. (see Appendix 2)

The AD8 is an 8-item questionnaire that operates on a binary scale (yes, a change/no change; along with a third unscored option of 'don't know') and asks the informant to indicate if a change has occurred in their friend/relative's cognition over the past 'several years'. Scores closer to 8 suggest greater cognitive impairment. (see Appendix 3)

Informant participants were asked to complete the questionnaires in relation to how the patient's cognition was just before their most recent stroke occurrence. Questionnaires were required to be completed within 1 month of patient hospital admission; however, this requirement was relaxed towards the end of

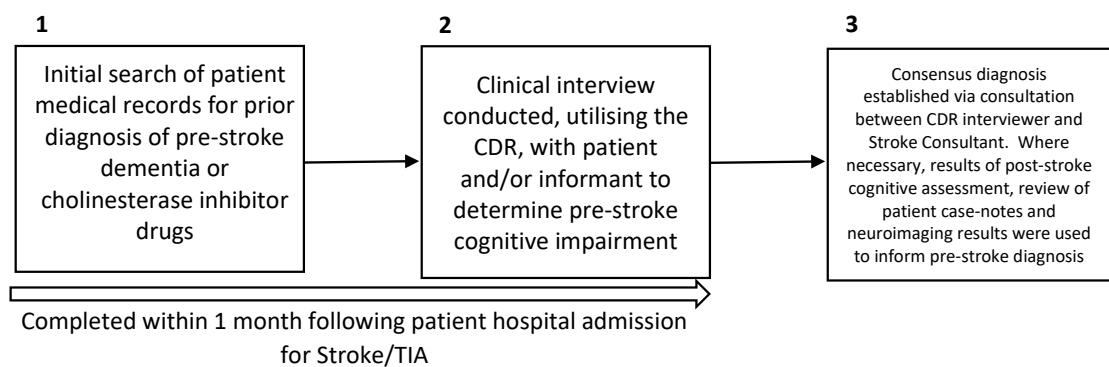
the study to assist participant recruitment. Questionnaires could be completed in the presence of the consenting researcher while the patient was still in hospital, or, if necessary, alone following patient discharge and returned via post.

3.2.5 Gold standard assessment

Dementia and mild cognitive impairment (MCI) were diagnosed according to DSM-IV criteria.(28)

Assessment of pre-stroke cognitive impairment was determined via a multicomponent assessment, and discussion between a researcher (MT) and stroke consultant (TQ). (See Figure 3-1)

Figure 3-1. Gold Standard assessment process



Following hospital admission for stroke, an initial examination of patient medical records was conducted to determine if patients had a formal diagnosis of dementia or were on cholinesterase inhibitor drugs before their presenting stroke occurred. If no prior diagnosis or drug use was present, a clinical interview, utilising the Clinical Dementia Rating scale (CDR), with the patient and/or the informant was conducted by a researcher (MT) with experience in dementia/MCI diagnosis and blinded to results of the informant questionnaires. The CDR is a structured interview that assesses patients for impairment across 6 domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). Scores on each domain are synthesized to establish a global CDR score. Interviews were conducted either face-to-face or via telephone where necessary. A CDR rating of 0 was defined as

‘no pre-stroke cognitive impairment’; 0.5 defined as ‘pre-stroke MCI present’; a rating of 1-3 defined as ‘pre-stroke dementia present’. Assessment was supplemented by a baseline and 1 month post-stroke cognitive assessment with the patient (conducted face-to-face only). This supplementary assessment involved the Abbreviated Mental Test-10 (AMT10)(126) (see Appendix 4), a mini-Montreal Cognitive Assessment (mini-MoCA)(127) (see Appendix 4), the Oxford Cognitive Screen (OCS)(128), a delirium assessment using the ‘Confusion assessment method for the Intensive Care Unit’ (CAM-ICU)(129), and examination of case-notes and neuroimaging results where possible (case-note access was only available for review by the researcher (MT) and stroke consultant (TQ) at the Glasgow Royal Infirmary, Queen Elizabeth University Hospital and Royal Alexandra Hospital). The AMT-10 is a 10-item brief cognitive assessment; it is scored out of 10 and scores of <8 suggest cognitive impairment is present. The mini-MoCA is a brief cognitive assessment and shortened version of the MoCA; it generates a score out of 12, with scores <10 suggesting cognitive impairment is present. The OCS is brief neuropsychological cognitive assessment battery that was designed to screen for cognitive impairment following stroke; it assesses numerous domains including memory, attention, language and praxis. The CAM-ICU is a brief delirium screening tool. Presence of delirium is defined based on an acute change in mental status, plus inattention, and either altered level of consciousness or disorder thinking.

Based on this information, a consensus diagnosis was reached via discussion between the interviewing researcher (MT) and a stroke consultant (TQ). If both the patient and/or informant were unavailable for clinical interview and access to patient medical/case-notes was unavailable, a gold standard diagnosis could not be established for the participant.

3.2.6 Clinical and demographic data

Patient level data was collected via a combination of medical records or patient self-report. Pre-stroke depression (major/minor depressive episode) and anxiety disorder (generalised anxiety disorder; panic disorder; agoraphobia/claustrophobia; social anxiety; specific phobia) was assessed via clinical interview with the patient and/or their informant, by an assessor (MT)

trained in using the ‘Structured Clinical Interview for Depression’ version 5 (SCID-5). All diagnoses of pre-stroke depressive/anxiety disorders were made in accordance with DSM-5 criteria. (30) The SCID was conducted at the same time-point as the CDR interview. Time-frame for mood and anxiety disorder covered was the 6 months before the stroke. The rationale behind this time-frame for assessment is outlined in chapter 5, section 5.2. Stroke severity was assessed via the National Institute of Health Stroke Scale (NIHSS),(130) using retrospective chart review.(131) Pre-stroke disability was assessed via the pre-stroke modified Rankin Scale (pre-stroke mRS).

3.2.7 Statistical analysis

3.2.7.1 Demographic comparison

I compared clinical and demographic data for patients recruited at the Glasgow Royal Infirmary who were included in the analysis of this sub-study against patients recruited at the Glasgow Royal Infirmary who were excluded from analysis (due to lack of informant). Group differences were compared for age, sex, pre-stroke mRS (dichotomised as disabled (≥ 2) vs non-disabled), stroke-type (dichotomised as lacunar vs non-lacunar), pre-stroke depression, number of medications, post-stroke aphasia, post-stroke delirium, stroke severity (NIHSS), diabetes and atrial fibrillation. Differences between the two groups were examined using one-way Analysis of Variance (ANOVA) for linear variables and Chi square for categorical variables.

3.2.7.2 Diagnostic test accuracy of Informant assessment

MedCalc version 18.11 was used for all analyses.

Performance of informant tools were assessed against the gold-standard diagnosis. I investigated the tools’ overall diagnostic accuracy, for both ‘dementia vs non-dementia’ and ‘any cognitive impairment vs no cognitive impairment’, via area under empirical ROC (AUROC) curves using the Delong et al., (1988) (132) method.

The most commonly applied published cut-point for the IQCODE in stroke is >3.4 ; (76) the AD8 is not frequently used in stroke but has a recommended published (and most commonly utilised) cut-point of ≥ 2 . (124) I constructed the tools' diagnostic properties at these cut-points using 2x2 tables. McNemar's test was used to statistically compare sensitivity and specificity values when the number of observations was >20 .

In addition, I determined if the apparent optimal cut-points for each tool matched the recommended published cut-points based on the point on empirical ROC curve nearest the top left-hand corner of the ROC graph. (81)

When data was missing from the informant questionnaire, the assessment was ruled invalid when >2 questions were not answered. If ≤ 2 questions were missing, I applied the average score to the 2 missing questions for the IQCODE, while missing AD8 responses were scored as 'No' responses. AD8 'don't know' responses were also treated as 'no' responses for scoring purposes.

A series of sensitivity analyses were conducted for all 'any cognitive impairment vs no cognitive impairment' analyses. I removed patients who were unable to complete a CDR interview and did not already have a formal diagnosis of dementia. I also examined if tool properties differed based on order of administration; removed cases in which the time-frame for informant assessment and/or CDR assessment was >31 days, and assessed if scoring missing/'don't know' responses on the AD8 as 'yes' responses altered the results.

3.3 Results

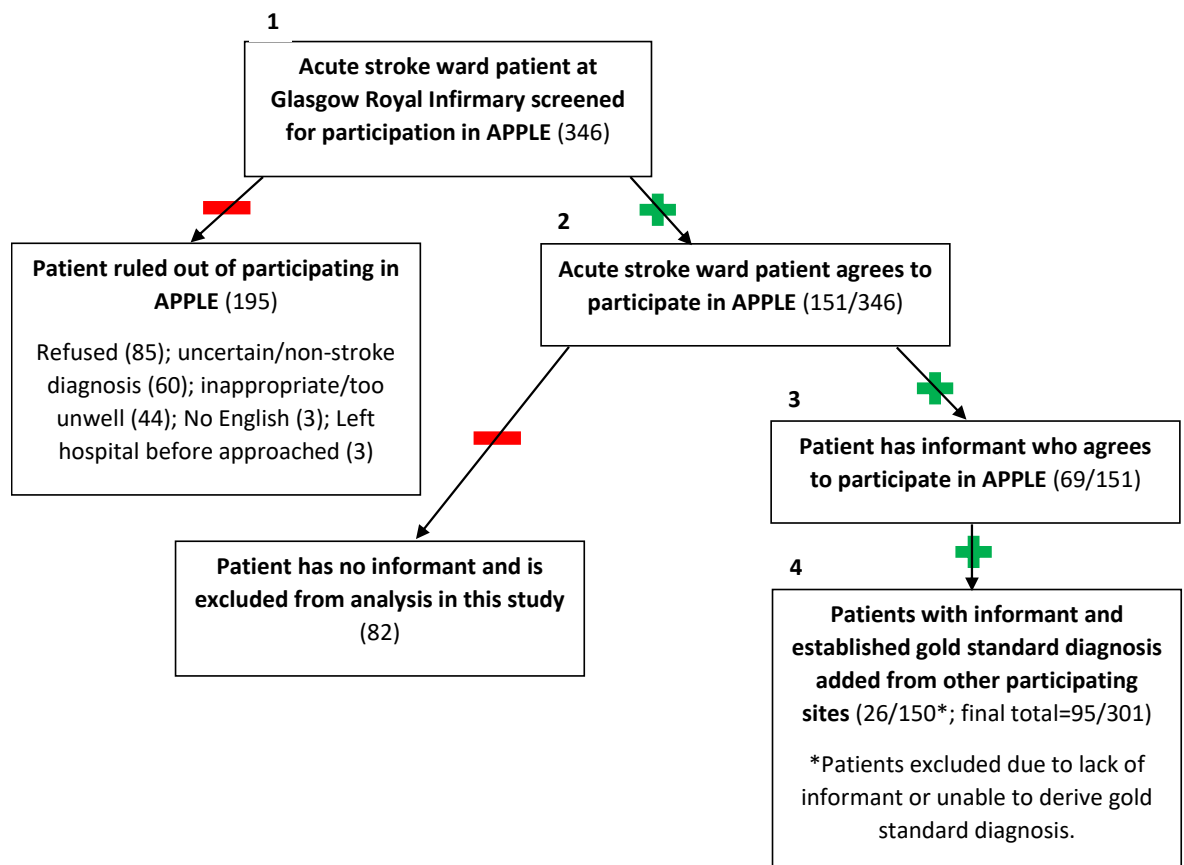
3.3.1 Diagnostic test accuracy of informant assessment

A total of 346 patients admitted to the Glasgow Royal Infirmary were considered for participation in the APPLE study. One hundred and fifty-one patients from the Glasgow Royal Infirmary agreed to participate in APPLE. Total numbers approached from all sites were not available; however, 301 patients across all

sites agreed to take part in the APPLE study (including the 151 recruited via the Glasgow Royal Infirmary). Two-hundred and five were excluded from analysis in this sub-study due to lack of an informant or gold standard assessment data, leaving a total of 95 patients with informants for analysis of IQCODE-SF and AD8 diagnostic test accuracy. Figure 3-2 outlines the recruitment process. Numbers for stage 1, 2 and 3 reflect recruitment at the Glasgow Royal Infirmary only; stage 4 reflects the total number of patients available for analysis following addition of recruited numbers from all other participating sites.

Clinical and demographic comparisons between those included in analysis vs those excluded from analysis (restricted to Glasgow Royal Infirmary only) suggest the two groups differed by stroke-type ($X^2=10.318$, $p=0.001$); specifically, excluded patients had a higher proportion of lacunar strokes [22] as compared to non-lacunar strokes [57] than those included (57 non-lacunar; 4 lacunar). There were no other differences in tested variables (all $p>0.05$).

Figure 3-2. Flow diagram of recruitment process (numbers in stages 1, 2 & 3 restricted to Glasgow Royal Infirmary only)



Six of the recruited patient participants who had no formal pre-stroke dementia diagnosis were evaluated for pre-stroke cognitive impairment via baseline post-stroke cognitive assessment results and case-note review data only. All other patient participants either had a formal diagnosis of pre-stroke dementia present in medical records or pre-stroke cognitive impairment diagnosis was established involving the CDR interview. All patient participants had AD8 data available (2 contained missing data but could still be utilised) and 94/95 (99%) had IQCODE-SF data available (1 contained substantial (>2 unanswered questions) missing data and was removed from analysis). Median time for completion of informant assessment following admission was 5 days (range=2-284); median time for completion of CDR assessment following admission was 7 days (range=2-284). Thirty out of 95 (31.5%) patients were cognitively impaired before their stroke according to gold-standard diagnosis (13 dementia; 18 MCI); 6/13 (46.1%) patients had a formal diagnosis of pre-stroke dementia. Population descriptive statistics can be seen in Table 3-1.

Table 3-1: Population descriptive statistics

Variable	Overall*
Age (Median; 25th-75th percentile)	73 (61-80)
Sex Male (%)	48/88 (54.5%)
Stroke-type (%)	
<i>Total Anterior Circulation Stroke</i>	7/82 (8.5%)
<i>Partial Anterior Circulation Stroke</i>	26/82 (31.7%)
<i>Lacunar Stroke</i>	9/82 (11.0%)
<i>Posterior Circulation Stroke</i>	22/82 (26.8%)
<i>Trans Ischaemic Attack</i>	18/82 (21.9%)
NIHSS (Median; IQR)	1 (0-4)
Pre-stroke modified Rankin Scale (nn; %)	
0	33/85 (38.8%)
1	14/85 (16.5%)
2	14/85 (16.5%)
3	19/85 (22.4%)
4	5/85 (5.9%)
Pre-stroke depressive disorder (nn; %)	21/95 (22.1%)
Pre-stroke anxiety disorder (nn; %)	6/95 (6.3%)
Post-stroke Delirium	2/95 (2.1%)
Post-stroke Aphasia (nn; %)	5/88 (5.7%)
Previous stroke	26/85 (30.6%)
Diabetes	16/80 (20.0%)
Atrial Fibrillation	14/82 (17.1%)
Medication count (Median; IQR)	7 (5-10)

*Data presented where available; reduced denominator reflects missing values for that category.

3.3.2 Diagnostic test accuracy data for IQCODE-SF and AD8

3.3.2.1 Any cognitive impairment vs no cognitive impairment

AUROC curves were 0.85 (95%CI=0.76-0.91), $p<0.01$, for IQCODE-SF and 0.82 (95%CI= 0.73-0.89), $p<0.01$, for AD8.

Sensitivity and specificity values for the IQCODE-SF for any cognitive impairment at cut-point >3.4 were 62.1% (95%CI=42.3%-79.3%) and 87.7% (95%CI=77.2%-94.5%) respectively. For AD8 at cut-point ≥ 2 , sensitivity was 86.7% (95%CI=69.3%-96.2%) and specificity 70.8% (95%CI=58.2%-81.4%). McNemar's test suggested the AD8 was significantly more sensitive to detecting any cognitive impairment than the IQCODE-SF (difference: 24.1%, 95%CI=5.9%-42.4%; $p=0.04$). Specificity of the IQCODE-SF was significantly greater than the AD8 (difference: 16.7%, 95%CI=6.7%-26.6%; $p<0.01$).

The optimal cut-point based on ROC curve analysis for IQCODE-SF was >3.06 , giving sensitivity and specificity values of 93.1% (95%CI=77.2%-99.2%) and 63.1% (95%CI=50.2%-74.7%), and ≥ 2 for AD8 (sensitivity and specificity values same as published recommended cut-point, described above). (See Figure 3-3)

Additional diagnostic properties, including positive predictive values, negative predictive values and likelihood ratios for both informant tools can be seen in Table 3-2.

Table 3-2: Diagnostic Test Accuracy Properties of the IQCODE -SF and AD8 for differentiating any cognitive impairment from cognitively normal

	AD8	IQCODE-SF
Positive likelihood ratio	2.96 (95%CI=1.98 to 4.44)	5.04 95%CI=2.48 to 10.24)
Negative likelihood ratio	0.19 (95%CI=0.07 to 0.48)	0.43 (95%CI=0.27 to 0.70)
Positive Predictive Value	57.8% (95%CI=47.76% to 67.20%)	69.2% (95%CI=52.56% to 82.05%)
Negative Predictive Value	92.0% (95%CI=82.01% to 96.67%)	83.8% (95%CI=76.33% to 89.28%)
Prevalence (pre-stroke cognitive impairment)	31.6% (95%CI=22.4% to 41.9%)	30.9% (95%CI=21.7% to 41.2%)

3.3.2.2 Dementia vs no dementia

AUROC for IQCODE-SF was 0.91 (95%CI=0.84-0.96), $p<0.01$ and 0.85 (95%CI=0.77-0.92), $p<0.01$ for AD8.

Sensitivity and specificity values for the IQCODE-SF for dementia vs no dementia at cut-point >3.4 were 91.7% (95%CI=61.5%-99.8%) and 81.7% (95%CI=71.6%-89.4%); AD8 at cut-point ≥ 2 had sensitivity 92.3% (95%CI=64.0%-99.8%) and 59.8% (95%CI=48.3%-70.4%) specificity. There were only 12 (following removal of 1 IQCODE-SF with substantial missing data) cases of dementia available for analysis of comparative sensitivity, hence formal statistical analysis via McNemar's test was not appropriate. Eighty-two observations were available for formal statistical comparison of specificity. McNemar's test suggested IQCODE-SF had significantly greater specificity than AD8 (Difference: 20.7%, 95% CI=11.3%-30.1%; $p<0.01$).

Optimal cut points suggested by ROC curve analysis were >3.4 for IQCODE-SF (sensitivity and specificity values same as at recommended published cut-point described above) and >3 for AD8 (sensitivity 92.3%, 95%CI=64.0%-99.8%; specificity 80.5%, 95%CI=70.3%-88.4%). (Figure 3-4)

Additional diagnostic properties for both informant tools can be seen in Table 3-3.

Table 3-3. Diagnostic Test Accuracy Properties of the IQCODE-SF and AD8 for differentiating dementia from no-dementia

	AD8	IQCODE-SF
Positive likelihood ratio	2.29 (95%CI=1.69 to 3.12)	5.01 (95%CI=3.08 to 8.17)
Negative likelihood ratio	0.13 (95%CI=0.02 to 0.85)	0.10 (95%CI=0.02 to 0.67)
Positive Predictive Value	26.7% (95%CI=21.1% to 33.1%)	42.3% (95%CI=31.0% to 54.4%)
Negative Predictive Value	98.0% (95%CI=88.1% to 99.7%)	98.5% (95%CI=91.1% to 99.8%)
Prevalence (pre-stroke dementia)	13.7% (95%CI=7.5% to 22.3%)	12.8% (95%CI=6.8% to 21.2%)

Figure 3-3. ROC curves and optimal cut-points for IQCODE and AD8 when discriminating between any pre-stroke cognitive impairment vs no pre-stroke cognitive impairment

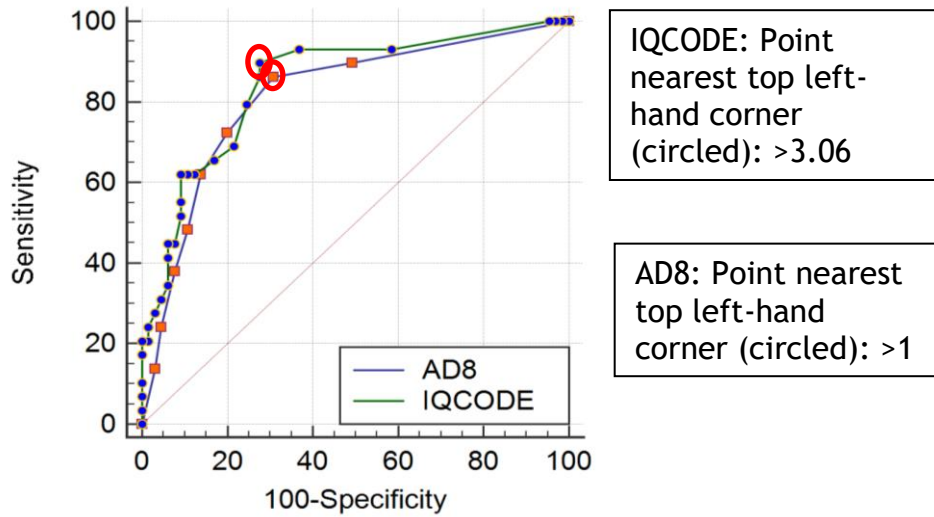
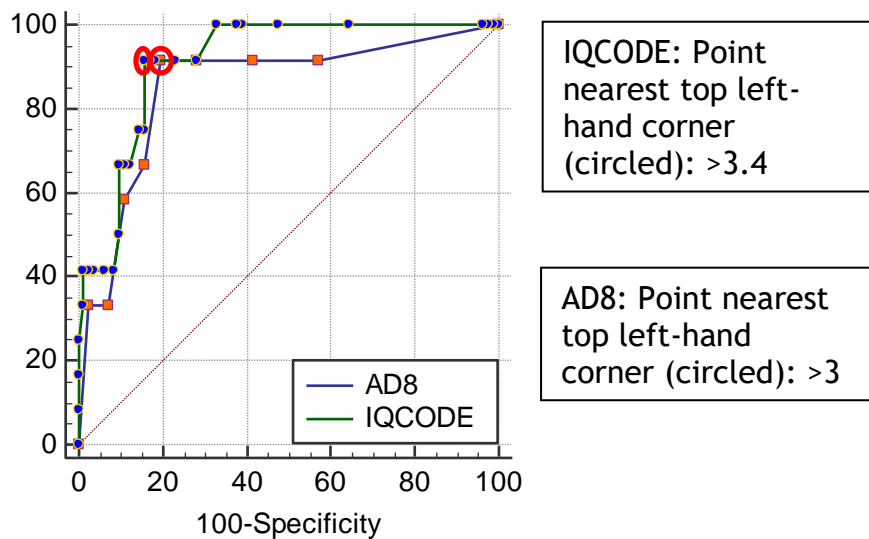


Figure 3-4. ROC curves and optimal cut-points for IQCODE and AD8 when discriminating between pre-stroke dementia vs no pre-stroke dementia



3.3.3 Sensitivity analysis

Removal of 6 cases in which the gold standard diagnosis was determined without CDR interview left 27 cases of pre-stroke cognitive impairment and 62 non-cognitively impaired patients for analysis. Reanalysis without these cases did not significantly alter the relationship between the tools' specificity. AD8 specificity= 72.6% (95%CI=59.8%-83.1%); IQCODE-SF specificity= 90.3% (95%CI=80.1%-96.4%) (size difference=12.9%, 95%CI=3.4%-22.4%; p=0.02); however, the difference in sensitivity was no longer statistically significant; AD8 sensitivity= 85.2% (95%CI=66.3%-95.8%), IQCODE-SF sensitivity= 61.5% (95%CI=40.6%-79.8%); size difference=23.1% (95%CI=3.7%-42.5%); p=0.07). AUROC curves for both tools were largely unaltered: AD8 AUROC=0.82 (95%CI=0.72-0.89), p<0.01; IQCODE-SF AUROC= 0.84 (95%CI=0.74-0.91), p<0.01.

The IQCODE-SF was completed first for 49/95 patients (16 cases of pre-stroke cognitive impairment); the AD8 completed first for 46/95 patients (14 cases of pre-stroke cognitive impairment). Comparison of assessment administration order did not alter the pattern of the differing sensitivity and specificity values of the IQCODE-SF and AD8. When completed first, IQCODE-SF sensitivity at cut-point >3.4 was 66.67% (95%CI=38.4%-88.2%), specificity was 94.1% (95%CI= 80.3%-99.3%), AUROC=0.87 (95%CI=0.75-0.95); AD8 sensitivity at cut-point ≥ 2 when completed second was 85.7% (95%CI=57.2%-98.2%), specificity was 74.3% (95%CI= 56.7%-87.5%), AUROC=0.82 (95%CI=0.68-0.91), p<0.01 . AD8 sensitivity when completed first was 90.9% (95%CI=58.7%-99.8%), specificity was 72.4% (95%CI=52.8%-87.3%), AUROC=0.83 (95%CI=0.69-0.92), p<0.01; IQCODE-SF sensitivity when measured second was 54.6% (95%CI=23.4% to 83.3%), specificity was 79.3% (95%CI=60.3%-92.0%), AUROC=0.82 (95%CI=0.67-0.91), p<0.01.

I also removed 13 cases in which the informant questionnaires and/or the gold standard clinical interview assessment took place >31 days following hospital admission. The pattern of sensitivity and specificity differences for both tools at recommended published cut-points remained the same. From a total of 82 AD8 cases and 81 IQCODE-SF (24 pre-stroke cognitive impairment), AD8 sensitivity

was 88.0% (95%CI=68.8%-97.5%), specificity was 71.2% (95%CI=57.9%-82.2%); IQCODE-SF sensitivity was 70.8% (95%CI=48.9%-87.4%), specificity was 91.5% (95%CI=81.3%-97.2%). McNemar's test suggested the difference in sensitivity was no longer significant after removal of these cases (difference=16.0%, 95%CI=-2.2%-34.2%; $p=0.22$); difference in specificity remained statistically significant (difference: 20.7%, 95%CI=10.3%-31.1%; $p<0.01$) AUROC values remained largely unchanged (AD8 AUROC: 0.83, 95%CI=0.73-0.90, $p<0.01$; IQCODE-SF AUROC: 0.87, 95%CI=0.78-0.94, $p<0.01$).

Finally, analysis was rerun with 'unknown' or missing responses for the AD8 scored as 'yes'; sensitivity (86.7%, 95%CI=69.3-96.2) and specificity (69.2%; 95%CI=56.6%-80.1%) values at recommended cut-points did not change; AUROC was also unchanged (0.82, 95%CI= 0.73-0.89; $p<0.01$).

3.4 Discussion

3.4.1 Diagnostic test accuracy of Informant assessment

My data suggests that both the AD8 and IQCODE-SF are valid tools for pre-stroke cognition screening in the acute stroke setting. Both tools performed significantly above chance level for discriminating between cognitively impaired and non-cognitively impaired patients and also between dementia and no-dementia; both tools demonstrated good (>0.8) overall discriminability for both patient groups. This is reassuring as employment of informant tools is a common approach for pre-stroke cognition assessment in both stroke research and clinical practice. (76)

The IQCODE-SF and AD8 have typically applied published cut-points of ≥ 3.4 and ≥ 2 respectively. Previous research (82) has suggested that the AD8 may be more sensitive to detection of dementia and mild cognitive impairment than the IQCODE at these cut-points.

I similarly found that the AD8 was significantly more sensitive to cognitive impairment than the IQCODE-SF at their most commonly applied cut-point, but I

found no evidence that it was more sensitive to dementia. This is not surprising as my 'cognitively impaired' group was predominantly made up of patients with MCI. The AD8 was originally designed to detect very mild dementia—equating to a CDR score of 0.5, which is also frequently applied to patients demonstrating MCI;(133) its recommended cut-point reflects that intent. The IQCODE on the other hand was developed to detect dementia-level cognitive impairment, with no explicit predisposition towards the milder end of the cognitive impairment spectrum. This may explain the observed discrepancy regarding the two tools' respective differences in sensitivity to dementia vs any cognitive impairment at recommended published cut-points.

These findings are consistent with the IQCODE's tendency to correlate with brief screening tests (which are also often insensitive to milder forms of cognitive impairment) over in-depth neuropsychological assessments (which tend to be more sensitive to mild cognitive impairment). (79) Typical utilisation of the IQCODE-SF at published cut-points in the stroke setting may therefore result in significant numbers of non-dementia level cognitively impaired patients passing unrecognised. On the other hand, the IQCODE-SF was significantly more specific than the AD8 to both any cognitive impairment and dementia; hence typical utilisation of the IQCODE-SF should produce fewer false positives.

While differences in sensitivity and specificity of the two tools are apparent at recommended cut-points, I would note that the overall (AUROC) diagnostic accuracy of the tools were comparable. This is consistent with previous research, which has reported similar AUROC values for the AD8 and IQCODE-SF. (82) These comparable AUROC values suggest that the observed differences in sensitivity and specificity could be balanced out via application of alternative cut-points. In this study, a cut-point of >3.06 appears optimal should the IQCODE-SF be utilised for assessing cognitive impairment in populations with high numbers of non-dementia level cognitive impairment; while the AD8 may perform better at a cut-point of ≥ 4 if the objective is to identify dementia only. However, while it is conceivable that alterations to cut-points may be beneficial when a tool is employed in a different population and context,(90) I would highlight that ostensible optimal cut-points often vary from study to study (123, 124) and variability in cut-point application is a source of the heterogeneity

commonly observed in stroke-cognition research. (76) Further work is therefore required in order to determine if there are alternative optimal cut-points for use of the IQCODE-SF and AD8 in stroke. For the time-being, I would suggest that clinicians and researchers do not diverge from the most commonly applied published cut-points, until more concrete recommendations can be made.

3.4.2 Clinical recommendations

The IQCODE-SF and AD8 appear to have contrasting properties when used at their recommended published cut-points. The IQCODE-SF is currently the preferred informant tool for assessing cognition in stroke (76) and is the more specific of the two tools; however, it is debatable whether sensitivity or specificity should be prioritised in cognitive screening. Early detection of cognitive impairment has been associated with improved quality of life and reduced need for care-home admission. (134) On the other hand, misdiagnosis can be highly distressing and must also be acknowledged.

While both the IQCODE-SF and AD8 may be able to achieve a high degree of sensitivity or specificity (depending on the cut-point applied), the AD8 is both shorter and easier to score—these are highly advantageous properties in a busy acute setting. The data does not allow for a definitive recommendation of one tool over the other; however, it is possible that AD8 may be more optimally suited for use in stroke than the more commonly used IQCODE-SF. This possibility requires further validation.

3.4.3 Strengths and limitations

I have conducted a highly inclusive study that is not limited by the strict exclusionary criteria that are typically applied in stroke research. I have followed best practice guidelines for conducting diagnostic test accuracy research and present results that have ‘real world’ clinical value. However, there are some important limitations that should be considered.

The sample size is small, and the majority of participants are from a single site; hence, these findings may not generalise to the wider stroke population. While

my comparison of clinical and demographic data for included vs excluded APPLE patients was reassuring (only differing by stroke-type), larger studies are needed to confirm our observations regarding informant tool diagnostic test accuracy performance in stroke.

The confidence intervals regarding the size of sensitivity difference between IQCODE-SF and AD8 for detecting any cognitive impairment when used at traditional cut-points are wide; it is possible that the difference between the two tools is as minor as 6%, which may not be clinically meaningful.

The gold standard assessment is imperfect and complicated by the retrospective nature of the assessment, as well as potentially confounded by cognitive complications of the stroke. Moreover, not all patients had a complete gold standard assessment as they were lacking a clinical interview and some patients were assessed longer than 1 month following stroke. My resultant sensitivity analyses altered the statistical significance level in the comparisons of sensitivity such that the observed difference was no longer significant at the traditional level of $p < 0.05$. However, this could be a consequence of the reduced statistical power, and the general pattern of higher sensitivity of the AD8 compared to the IQCODE-SF remained.

Finally, while blinding to questionnaires was enforced to minimise bias, the informant participated in the gold-standard assessment via CDR interview. As such, it is uncertain to what extent informant answers to CDR interview questions may have been biased by prior completion of the questionnaire or vice-versa.

3.5 Conclusions

The IQCODE-SF and AD8 are both valid measures of pre-stroke cognitive impairment in the acute stroke setting. However, the AD8's shorter duration, ease of scoring, and possible heightened sensitivity to non-dementia level cognitive impairment at the recommended published cut-point may make it more suited to the busy acute stroke unit than the IQCODE-SF. Further work is

required to confirm these observations as well as to determine if alternate cut-points exist for optimal utilisation of these tools in acute stroke.

Chapter 4. Pre-stroke depression: a systematic review and meta-analysis of prevalence and risk association with post-stroke depression.

4.1 Introduction

As discussed in chapter 2, section 2.2, in order to better understand the natural history and mechanistic development of post-stroke depression, it is important to have an understanding of pre-stroke depressive problems. However, prevalence rates of pre-stroke depression are not well established, and the reported risk association is inconsistent. We currently have little insight as to the reasons for this inconsistency.

In a literature that is seemingly disparate with potentially biased papers, a comprehensive review, critical appraisal and synthesis can aid our understanding of the topic. The primary aim of this review was to summarise the prevalence of pre-stroke depression reported across the literature. The secondary aim was to summarise the association between pre-stroke depression and post-stroke depression.

4.2 Method

A systematic review of the literature based upon a pre-registered protocol (PROSPERO identifier: CRD42017065544) was conducted. All aspects of planning, conduct and reporting were guided by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) consensus statement. (135) All aspects of title searching, data extraction and risk of bias assessment were performed by two independent researchers trained in systematic review (MT, OM). Decisions were made by consensus with recourse to a third arbitrator as necessary (TQ).

4.2.1 Search Strategy

Initial scoping of the literature suggested that pre-stroke depression was rarely the primary focus of original research and was more often described as a co-variate in studies that investigate post-stroke mood disorder. Thus, my search strategy adopted two complementary approaches to the literature. A specific search with a focus on pre-stroke depression was performed (search A) as well as a more sensitive search with a focus on post-stroke depression, to identify papers from which data on pre-stroke depression could be obtained (search B; see Appendix 7).

As the emphasis was on published, peer-reviewed journals, I did not search grey-literature beyond the scope of the included search engines and hand searches. There were no restrictions placed on the basis of language; however foreign-language studies were only included if they could be translated into English.

Search A: A search syntax incorporating commonly used terms to describe pre-stroke depression (see Appendix 5) was created and multidisciplinary databases across a variety of platforms were searched: Medline (OVID), Embase (OVID), PsychInfo (EBSCO), Web of Science (Thomson Reuters), Cinahl (EBSCO) from inception to July 2017. This was supplemented by hand searches of references of identified papers and relevant reviews.

Search B: For the review of post-stroke depression, I used a search strategy that had informed a recently published systematic review on the topic. (59) Studies and relevant reviews identified via the search were hand searched for additional studies. I then screened the studies reporting prevalence of pre-stroke depression.

4.2.2 Inclusion/Exclusion criteria

Study designs: Observational studies, published in peer reviewed journals, that had a focus on mood, and that reported pre-stroke depression prevalence were included. The focus was on studies assessing pre-stroke depression

retrospectively, and over a period that could reasonably be thought to encapsulate life-course depression prevalence.

As I was interested in the natural population frequency of pre-stroke depression, any studies that recruited exclusively from clinical trials or that artificially enriched the population with 'cases' to allow matched case-control analyses were not included. Studies that prospectively assessed depression at a pre-stroke baseline and then followed patients up until an index stroke were also excluded if they did not assess depression at least every 2 years or more. Due to the typically sporadic time-frame covered for assessment of depression before stroke occurrence, prolonged periods with no assessment are liable to underestimate overall pre-stroke depression prevalence by systematically missing interim incident depression.

Exposures: Studies were accepted if they defined depression according to recognised clinical criteria that were current at the time of the primary paper (for example, Diagnostic and Statistical Manual of Mental Disorders version III/IV; International Classification of Diseases version 10); or if they defined depression using a cut-off point on a validated scale designed for assessing depression or depressive symptoms. Any defined form of depression, including minor depression, was included. Due to the often lax reporting of pre-stroke depression, it can be unclear how a study has defined the depression prevalence that they present (e.g. DSM IV major depression prevalence only or a combination of major depression, minor depression and dysthymia). Therefore, where studies did not operationalise the pre-stroke depression definition, but defined post-stroke depression consistent with our criteria, the pre-stroke depression data were included and coded on the assumption that pre-stroke depression was defined according to the same criteria that was applied for post-stroke depression. Moreover, data were included if the pre-stroke depression assessment method employed was likely to include a definition that was consistent with the described criteria (e.g. utilisation of medical records to determine a prior clinical diagnosis of 'depression'; self-report of a prior clinical diagnosis of 'depression').

Patients/participants: Studies were included where patients had a stroke or Transient Ischaemic Attack (TIA) of any form consistent with the World Health Organisation (WHO) definition. (136) Studies were excluded if they: 1) excluded patients with depression; 2) were restricted to a selected stroke cohort (e.g. females only; highly restricted age groups); 3) had mixed populations (e.g. stroke and non-stroke populations in study sample) unless the stroke specific data could be extracted separately; 4) only used antidepressant prescription as evidence of depression; 5) if the depression rates could not be separated from other mental health disorders (e.g. “psychiatric history”); 6) had excessively non-generalisable exclusion criteria (e.g. exclusion of vascular risk factors, such as hypertension or diabetes, common to the typical stroke population).

4.2.3 Study selection

Studies identified from electronic databases were exported to Covidence software (version 1.0, Veritas Health Innovation, Australia) for screening. After de-duplication, titles and abstracts were screened for relevance. Potentially relevant full texts were reviewed against the inclusion/exclusion criteria. To assess validity of the search strategy, a third researcher (TQ) who was independent of the search pre-specified five important papers or reviews that were relevant to the pre-stroke depression topic - Ayerbe et al., (2013) (59); De Ryck et al., (2014) (67); Hackett et al., (2005) (137); Robinson & Jorge., (2016) (62); Reid et al., (2010) (97). Validity was assessed by describing how many of these titles were returned on initial searching.

4.2.4 Assessment of risk of bias

Risk of bias (RoB) was assessed at study level. The potential important biases vary for my two review aims, so I used differing approaches to RoB assessments for each. For the first aim of describing prevalence of pre-stroke depression, I utilised the Critical Appraisal Skills Programme (CASP) cohort study tool, adapting it for our purpose. Specifically, I judged potential RoB based upon the focus of the paper, cohort recruitment method, stroke diagnosis method, pre-stroke depression assessment method and study population inclusion/exclusion criteria.

For the secondary aim of describing association between pre-stroke depression and post-stroke depression, a stroke-specific RoB assessment tool was adopted for use in studies describing risk factors. (138) This tool assessed RoB according to the following criteria: covariates controlled for; event-covariate ratio; control for collinearity; and, as a secondary category, I incorporated control for post-stroke care pathway. Rationale for our model assessment can be seen in Appendix 6.

4.2.5 Data extraction and analyses

The reported numbers of patients with pre-stroke depression along with the total sample size, setting, time-frame covered, country, first ever stroke (yes/no), means for assessment of pre-stroke depression, and definition of pre-stroke depression were extracted from each study. Where studies defined multiple forms of pre-stroke depression in their sample (e.g. major depression, minor depression, dysthymia), each subtype of depression was grouped together to form one whole depression sample. Additional data regarding post-stroke depression assessment method and covariates controlled were extracted only for studies included in my investigation into the risk association between pre-stroke and post-stroke depression.

All data were extracted to a pre-specified template and stored on an electronic spreadsheet (Excel, version 2016, Microsoft, USA). Where data were not available from the primary paper, author teams were contacted.

Meta-analyses were conducted using Comprehensive Meta-Analysis software version 3 (Biostat, USA).

The primary meta-analysis was designed to give a summary estimate of prevalence of pre-stroke depression. Due to my expectation that the true pre-stroke depression prevalence rate would vary within the population, I created a random-effects model to generate a pooled estimate of prevalence.

The second meta-analysis pooled adjusted odds ratios and confidence intervals of pre-stroke depression association with post-stroke depression from all studies utilising multiple regression analysis into a random effects model.

Heterogeneity was assessed through visual inspection of forest plots and by describing I^2 .

Publication bias for pre-stroke depression/post-stroke depression association analysis was determined by visually examining a funnel plot.

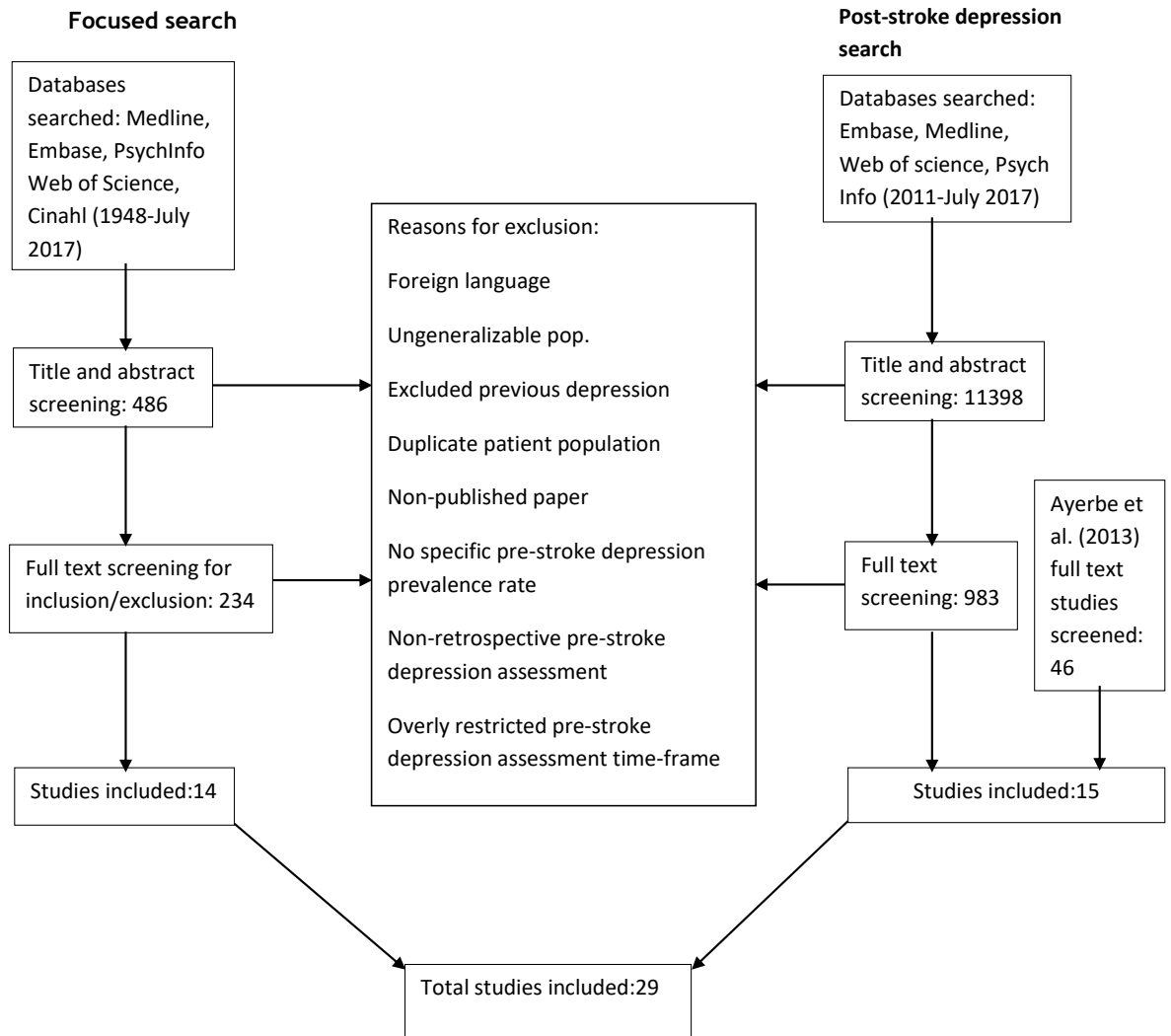
The overall strength of the summary data on prevalence rates and the pre-stroke depression/post-stroke depression association was judged using GRADE (The Grading of Recommendations Assessment, Development and Evaluation) criteria. (139)

Pre-specified subgroup analysis describing the effect of method of assessment for pre-stroke depression on prevalence rate was conducted. Studies were separated by assessment and data pooled where the assessment method utilised had relevant data from a minimum of five studies. Random-effects ANOVA was run, to explore the contribution of assessment method to observed heterogeneity of reported prevalence rates between studies.

If any study was overly influential on pooled pre-stroke depression rate or odds ratios, and presented 'outlier' data then sensitivity analysis was performed, removing the outliers and re-running the analyses. I also conducted pooled-prevalence-related sensitivity analyses based on time-frame covered in studies, utilisation of a screening method only to assess pre-stroke depression, and type of depression included within the sample (e.g. major depression only).

Figure 4-1 Outlines the study screening process.

Figure 4-1. Flow chart of Systematic search



4.3 Results

After excluding duplicates, our combined searches identified a total of 11884 studies. A total of 29 studies (93, 95, 96, 99, 100, 140-163) met the inclusion criteria (164993 patients; see Table 4-1). I requested additional data from seven authors and received data from one (Acknowledgements). Validity of my search strategy was supported as all pre-specified papers were identified in the initial search.

Table 4-1. Summary of included studies describing pre-stroke depression

Citation	Pre-stroke depression assessment method	Time period of depression assessment covered	Study setting	Country	First ever stroke population	Pre-stroke depression prevalence/total sample size
Aben et al., (2006)	Clinical interview	Not stated	Outpatient	Netherlands	Yes	41/189 (22%)
Barra et al., (2016)	Medical records	Not stated	Hospital/Rehab*	Norway	No	11/393 (3%)
Caiero et al., (2006)	Medical records	Life-time	Hospital/Rehab*	Portugal	No	38/178 (21%)
Castellanos-Penido et al., (2011)	Informant report	not stated	Hospital/Rehab*	Spain	No	13/89 (15%)
De Ryck et al., (2013)	1)Self-report 2)Medical records/charts 3)Screening (CESD+)	1) & 2) life history 3) 1 week prior to stroke	Hospital/Rehab*	Europe	No	30/125 (24%)
Dou et al., (2015)	Self-report	Not stated	Hospital/Rehab*	China	No	37/271 (14%)
Gillen et al., (2001)	Informant report	Life history	Hospital/Rehab*	USA	No	35/243 (14%)
Hackett et al., (2006)	Self-report	Not stated	Community	New Zealand	No	90/739 (12%)
Jorgensen et al., (2016)	Medical records	Up to 5 years prior to stroke	Community	Denmark	Yes	37426/157243 (24%)
Kim et al., (2014)	Self-report	Not stated	Hospital/Rehab*	Korea	No	17/423 (4%)
Kocer et al., (2011)	1)Clinical interview 2)Medical records	1) previous 1year 2) previous 10 years	Hospital/Rehab*	Turkey	No	27/148 (18%)
Kootker et al., (2016)	Medical records/charts	Not stated	Hospital/Rehab*	Netherlands	No	17/331 (5%)
Liu et al., (2017)	Self-report	Not-stated	Hospital/Rehab*	China	No	2/562 (0.4%)
McCarthy et al., (2016)	1)Medical records 2)Self-report	Not stated	Community	USA	No	43/322 (13%)
Ng et al., (1995)	Clinical Interview	Not stated	Hospital/Rehab*	Singapore	No	12/52 (23%)
Paolucci et al., (2006)	Self-report	Not stated	Hospital/Rehab*	Italy	No	90/1064 (8%)

Pohjasvaara et al., (1998)	Medical records	Not stated	Hospital/Rehab*	Finland	No	52/277 (19%)
Prisnie et al., (2016)	1)Self-report 2)Some via clinical interview	1) Not stated 2) life history	Outpatient	Canada	No	29/122 (24%)
Schottke et al., (2015)	Clinical interview	Life history	Hospital/Rehab*	Germany	No	31/289 (11%)
Sienkiewicz-Jarosz et al., (2010)	Medical records	Not stated	Community	Poland	Yes	20/242 (8%)
Singh et al., (2000)	Self-report	Not stated	Community	Canada	Yes	13/81 (16%)
Slater et al., (2012)	Medical records	Not stated	Hospital/Rehab*	Canada	No	22/123 (18%)
Tang et al., (2005)	Medical records	Not stated	Hospital/Rehab*	China	No	7/189 (4%)
Tang et al., (2011)	1)Self-report 2)Medical records	Not stated	Hospital/Rehab*	China	No	17/591 (3%)
Tse et al., (2017)	Screening (CIDI)#	Life-history	Hospital/Rehab*	Australia	No	20/98 (20%)
Verdelho et al., (2004)	1)Medical records 2)Self-reports	Not stated	Hospital/Rehab*	France	No	18/108 (17%)
Vermeer et al., (2017)	Self-report	Not stated	Outpatients	Canada	No	12/202 (6%)
White et al., (2014)	Medical records	Not stated	Hospital/Rehab*	Australia	No	16/134 (12%)
Zhang et al., (2010)	1)Clinical interview 2)Self-report	Life history	Hospital/Rehab*	China	No	28/165 (17%)

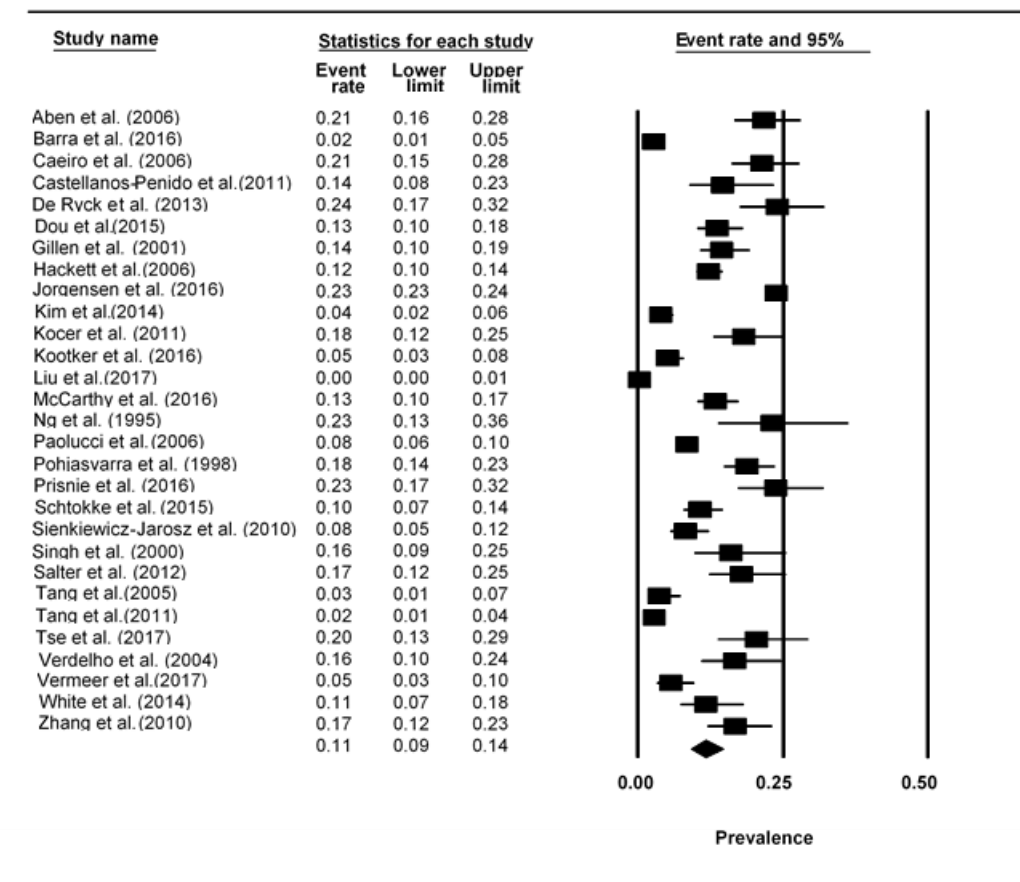
*Acute Hospital or Rehabilitation hospital; #CIDI=Composite International Diagnostic Interview; *CESD= Centre for Epidemiological Studies Depression.

4.3.1 Prevalence of pre-stroke depression

Pooled prevalence of pre-stroke depression was 11.6% (95%CI=9.2%-14.7%; 29 studies; total participants n=164993). There was substantial heterogeneity across studies ($I^2=95.8$). (see Figure 4-2)

RoB assessment of studies suggested potential bias in reported pre-stroke depression rates in all included studies. (see Table 4-2) Particular issues were around validity of the pre-stroke depression assessment (25 studies (83%) were at high or uncertain risk of bias) and external validity of the included participants (25 studies (83%) were at high or uncertain risk of bias), the latter primarily due to excluding patients with pre-stroke dementia/cognitive impairment (13 studies; 44%). Seventeen (59%) studies had an uncertain risk of bias in stroke assessment.

Figure 4-2. Forrest plot of pooled pre-stroke depression prevalence



Meta Analysis

Footnote: The plot indicates variability in reported prevalence rates between studies and an overall pooled prevalence of 11%.

Table 4-2. Risk of bias assessment for studies describing prevalence of pre-stroke depression

Citation	Focus on pre-stroke depression	Acceptable recruitment	Acceptable stroke assessment	Acceptable pre-stroke depression	Population risk of bias
Aben et al. (2006)	●	●	●	●	●
Barra et al. (2016)	●	●	●	●	●
Caiero et al. (2006)	●	●	●	●	●
Castellanos-Penido et al. (2011)	●	●	●	●	●
De Ryck et al. (2013)	●	●	●	●	●
Dou et al. (2015)	●	●	●	●	●
Gillen et al. (2001)	●	●	●	●	●
Hackett et al. (2006)	●	●	●	●	●
Jorgensen et al. (2016)	●	●	●	●	●
Kim et al. (2014)	●	●	●	●	●
Kocer et al (2011)	●	●	●	●	●
Kootker et al. (2016)	●	●	●	●	●
Liu et al. (2017)	●	●	●	●	●
Mcarthy et al. (2016)	●	●	●	●	●
Ng et al. (1995)	●	●	●	●	●
Paolucci et al. (2006)	●	●	●	●	●
Pohjasvarra et al. (1998)	●	●	●	●	●
Prisnie et al. (2016)	●	●	●	●	●
Schottke et al. (2015)	●	●	●	●	●
Sienkiewicz-Jarosz et al. (2010)	●	●	●	●	●
Singh et al. (2000)	●	●	●	●	●
Slater et al. (2012)	●	●	●	●	●
Tang et al. (2005)	●	●	●	●	●
Tang et al. (2011)	●	●	●	●	●
Tse et al. (2017)	●	●	●	●	●
Verdelho et al. (2004)	●	●	●	●	●
Vermeer et al. (2017)	●	●	●	●	●
White et al. (2014)	●	●	●	●	●
Zhang et al. (2010)	●	●	●	●	●

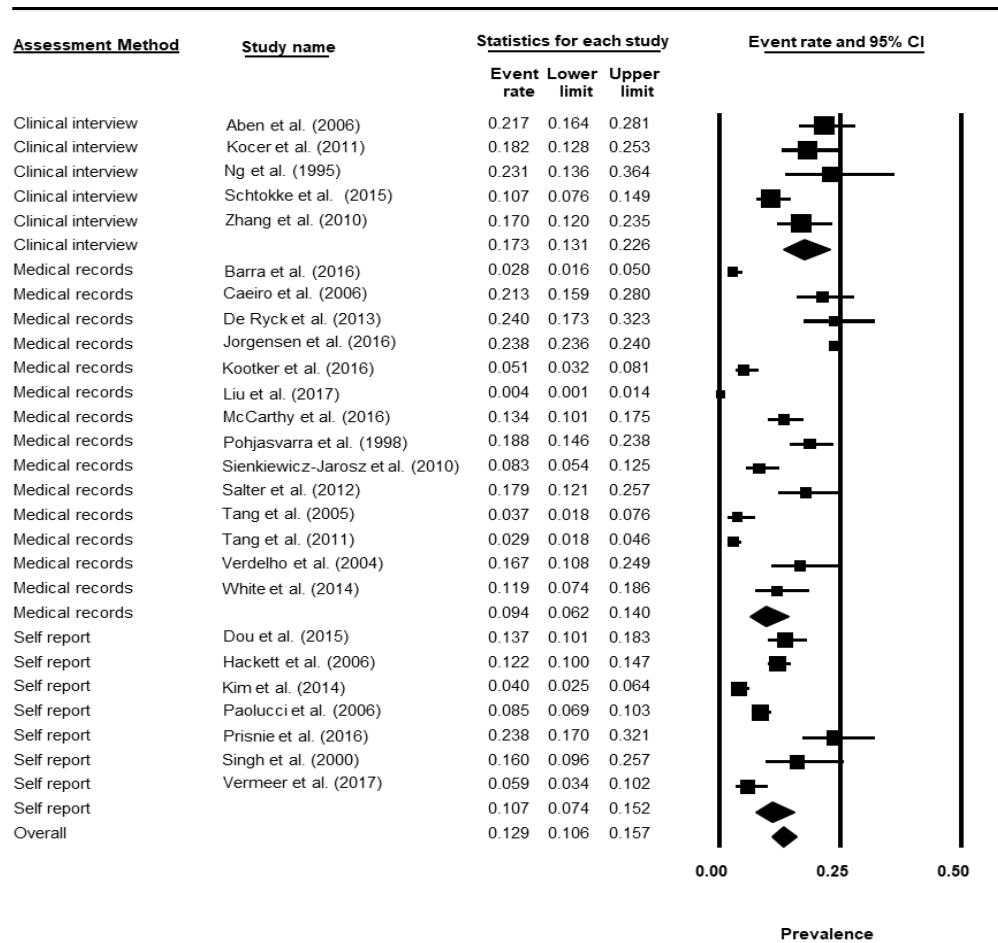
Colour code: High risk of bias; unclear risk of bias; low risk of bias

GRADE evaluation suggested that the strength of evidence to support my summary estimate of prevalence was ‘very low’ (see Appendix 7).

There was substantial variation in the method of pre-stroke depression assessment employed across studies. Pre-stroke depression was assessed using at least five different methods; eight studies utilised more than one method for assessing depression (see Table 4-1). The most commonly used methods were medical records/charts (utilised in 14 studies) and self-reports (utilised in 12 studies). The standard of reporting of assessment method within studies was mixed; most studies provided only minimal details of assessment method employed.

I described summary estimates of pre-stroke depression based on assessment method for self-reports, medical records/charts and clinical interviews. Prevalence was 10.7% (95%CI=7.4%-15.2%); 9.4% (95%CI=6.2%-14.0%) and 17.3% (95%CI=13.1%-22.6%) respectively (see Figure 4-3). Random-effects ANOVA suggested that method of assessment was an important contributor to between-study heterogeneity ($P=0.02$).

Figure 4-3. Forrest plot of prevalence by assessment method



Meta Analysis

Footnote: The plot indicates heterogeneity in prevalence rates across all assessment types. Pooled prevalence rates for self-reports and medical records are very comparable and both considerably lower than pooled rate of studies utilising clinical interview methodology.

4.3.2 Sensitivity analysis

No outliers were apparent in the analyses; however, three studies were identified that were restricted in duration of pre-stroke assessment (i.e. ≤ 1 year) and hence had been excluded, but otherwise met my inclusion criteria. (164-166) Sensitivity analysis was performed by inserting these three studies into my primary pre-stroke depression prevalence meta-analysis; the resultant pooled rate (11.8%; 95%CI= 9.6-14.5,) suggests that excluding such studies had minimal impact upon our reported rate. In addition, as one study(160) established a pre-stroke depression prevalence rate via a screening method, which could be more indicative of depressive symptoms, rather than depression

per se, I performed sensitivity analysis by removing this study; resultant pooled rates (11.4%; 95%CI= 8.9%-14.5%) suggest inclusion of this study did not bias my analysis. Only two studies explicitly reported that they limited their reported sample to major depression only (95, 149); hence I also removed these two studies. Again, resultant pooled rate (11.4%; 95%CI= 8.9%-14.6%) suggests that restriction to major depression only had minimal impact upon overall pooled rate.

4.3.3 Association with post-stroke depression

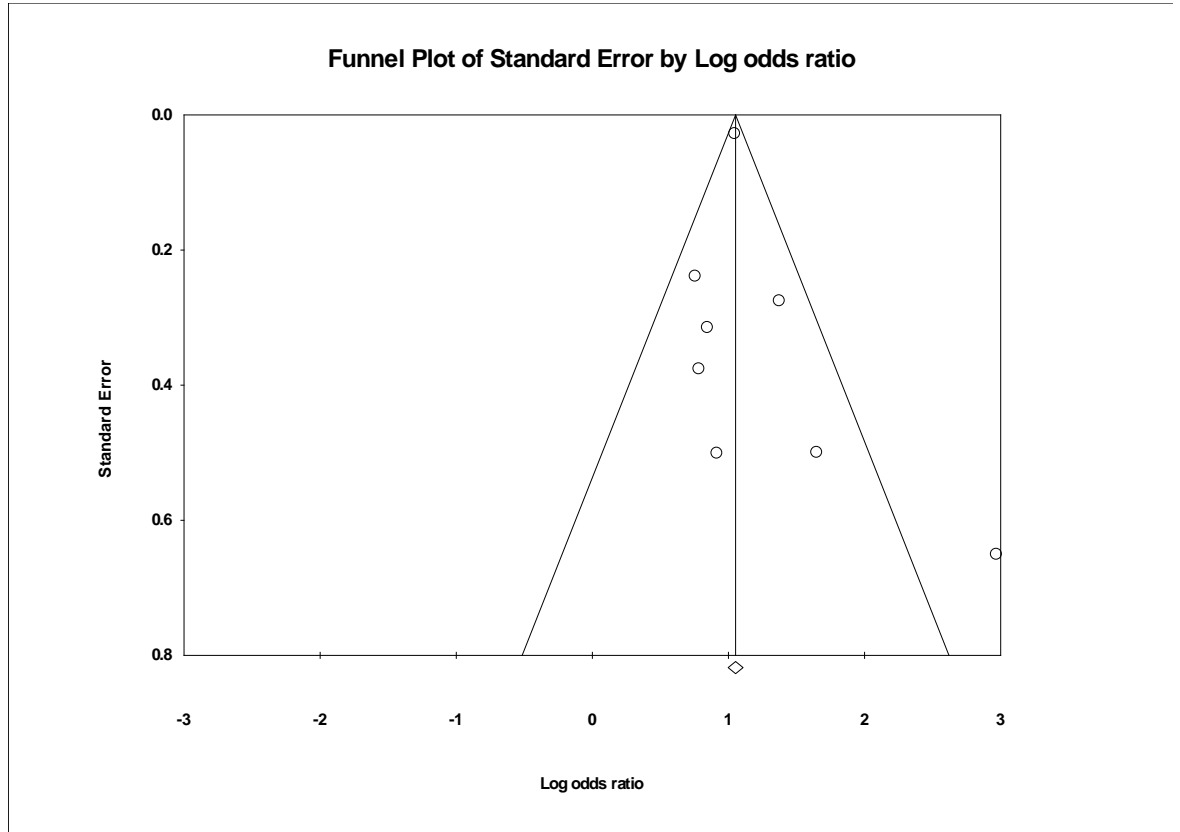
The association between pre and post-stroke depression was described in 24 studies (83%); (see Appendix 8) 14 (58%) reported significant associations. (see Appendix 8) Multiple logistic regression analyses were described in 15 studies (see Appendix 8) and 11 (73%) reported significant associations. (see Appendix 10) The resulting funnel plot did not suggest publication bias. (see Figure 4-4) Assessment methods employed to assess pre and post-stroke depression were variable, as were chosen covariates included in regression models. (see Appendix 9)

The papers describing association models were at risk of bias (see Table 4-3). In particular, no studies controlled for post-stroke care-pathway. Three out of four studies employing multiple regression models that failed to observe a risk association were underpowered (96, 140) or failed to control for important covariates (95); one study had a very small pre-stroke depression prevalence. (141)

Odds ratio data were available for nine studies in total. However, one study (100) was removed from analysis due to a lack of symmetry of log values. This left eight studies with a combined sample size of 37483 for meta-analysis. Random-effects analysis suggested a pooled odds ratio of 3.03 (95% CI of 2.30-3.98) (Figure 4-5). One study (159) appeared to be a clear outlier; hence sensitivity analysis was performed by removing this study and rerunning analysis. This did not meaningfully alter the strength of association (2.85; 95%CI=2.70-3.02).

GRADE evaluation suggested that the strength of evidence to support our summary estimate of association was ‘very low’ (see Appendix 10).

Figure 4-4: Funnel plot assessing publication bias of odds ratio data reported in studies



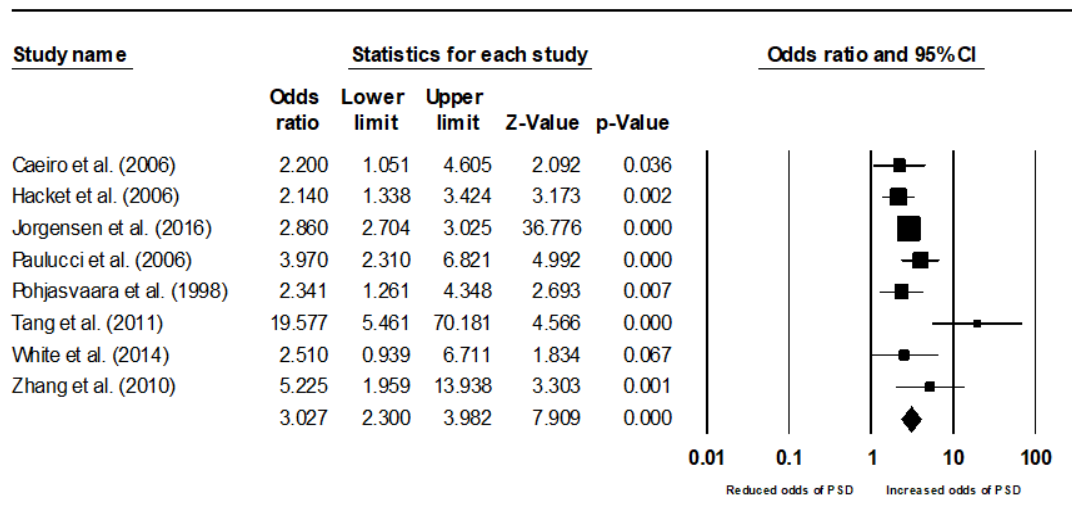
Footnote: The relatively symmetric pattern of odds ratio data suggests no publication bias is present.

Table 4-3. Risk of bias assessment of multiple logistic regression models employed to evaluate pre-stroke depression/post-stroke depression association

Citation	Common Covariates controlled for (post-stroke function/stroke severity)	Event-ratio size acceptable	Stepwise or collinearity controlled for	Care pathway covariate controlled for
Aben et al. (2006)	●	●	●	●
Barra et al. (2016)	●	●	●	●
Caiero et al. (2006)	●	●	●	●
De Ryck et al. (2013)	●	●	●	●
Hackett et al. (2006)	●	●	●	●
Jorgensen et al. (2016)	●	●	●	●
Mcarthy et al. (2016)	●	●	●	●
Ng et al. (1995)	●	●	●	●
Paolucci et al. (2006)	●	●	●	●
Pohjasvarra et al. (1998)	●	●	●	●
Schottke et al. (2015)	●	●	●	●
Tang et al. (2011)	●	●	●	●
Verdelho et al. (2004)	●	●	●	●
White et al. (2014)	●	●	●	●
Zhang et al. (2010)	●	●	●	●

Colour code: High risk of bias; low risk of bias

Figure 4-5. Forrest plot of odds ratios for developing post-stroke depression (PSD) based upon presence of pre-stroke depression



Meta Analysis

Footnote: Forrest plot shows a general consistency that pre-stroke depression increases odds of post-stroke depression. Pooled odds ratio indicates odds of post-stroke depression increase by 3 when pre-stroke depression is present.

4.4 Discussion

4.4.1 Prevalence

The primary aim of this review was to describe the natural stroke population prevalence of pre-stroke depression based upon data from typical stroke settings. My results suggest a pooled pre-stroke depression prevalence rate of ~12%, which is identical to the 12% mood disorder prevalence rate most commonly reported in the general population. (167) This is somewhat surprising given that depression is a risk factor for stroke. (168) Pre-stroke depression was assessed in diverse ways across studies and that there was a significant trend towards increasing prevalence with increasing complexity of testing. This indicates that the more one looks for pre-stroke depression, the more it is discovered, which is in keeping with research suggesting variable detection of pre-stroke depression according to assessment method employed. (98, 100, 154, 163) On this basis, the 17% pre-stroke depression rate, evident when in-depth

interviews were utilised to investigate presence of pre-stroke depression, may be more reflective of the actual pre-stroke depression prevalence, existent within the stroke population.

Comparing pre-stroke depression rates (17%) to recent estimates of post-stroke depression (39-52%) (59) demonstrate that rates of depression after stroke are several multiples higher than the rates of depression present before a stroke. These results suggest that the majority of cases of post-stroke depression are not simply the re-manifestation or ‘unmasking’ of pre-stroke depression. My findings are therefore in line with suggestions that the majority of cases of post-stroke depression are the product of the experience and consequences of the stroke itself. (59)

4.4.2 Risk Association

As a secondary aim, I described the association between pre-stroke depression and post-stroke depression. Recent findings prompted suggestions that the pre-stroke state is “not a meaningful predictor” of depression after stroke.(95) My meta-analysis results suggest that pre-stroke depression at any point over the life-time increases odds of post-stroke depression by as much as 3.0 (95%CI=2.3-4.0), when compared to those without pre-stroke depression. Notably, of the fifteen studies that utilised multiple logistic regression analysis to investigate the association, two of the four studies that failed to find an association were underpowered in their event-per variable ratio; (96, 140) one study (95) failed to control for important covariates, and one reported a very low rate of pre-stroke depression. (141) I would therefore suggest it is inaccurate to conclude that the pre-stroke state is not a meaningful predictor of depression after stroke and would encourage researchers to include pre-stroke depression as a case-mix adjuster in all future studies of post-stroke depression.

4.4.3 Strengths and Limitations

I present a methodologically robust synthesis of the published literature, following best practice in conduct of observational systematic review. However, quality of primary data mandated a low GRADE rating: prevalence rates reported

across studies were heterogeneous and studies had risk of bias. Specifically, the limitations of the available papers may risk underestimating pre-stroke depression rates. Particular issues were regarding sensitivity of pre-stroke depression assessment and exclusion of patients with pre-stroke cognitive impairment. The pooled rate may alternatively be *inflated* by inclusion of rates that reflect depressive symptoms rather than depression *per se*; although, my sensitivity analysis indicates that such rates were not overly influential towards the pooled prevalence that I report. More significantly, I cannot say for certain what form of depression the pooled rate describes, as explicit definitions of pre-stroke depression were lacking. Typically employed assessment methods (i.e. medical records, self-reported prior diagnosis, clinical interview) could conceivably incorporate any form of clinical depression (e.g. major depression, minor depression and dysthymia all inclusive), or may be predominantly constrained to major depression only. Clearer reporting in this regard would benefit the field.

Similarly, my assessment of the pre-stroke/post-stroke depression association has methodological limitations. Authors may have been more likely to give odds-ratios where an association was apparent; hence our summary quantitative analysis is at risk of reporting bias, albeit this was not evident in the corresponding funnel plot. Studies were heterogeneous in both covariates controlled for and assessment method utilised for both pre and post-stroke depression assessment, which could potentially bias or confound reported associations; for instance, strength of reported odds ratios may be heightened or diluted due to differences in control for stroke severity, or ability to accurately detect pre-stroke depression within a sample. Taking all this into account, my GRADE estimate of confidence in this evidence was 'very low'. I would also note that no included studies controlled for the possible influence of alterations in care pathway following assessment of pre-stroke depression. It seems plausible that recording pre-stroke depression, clinically, would result in greater use of pharmacological treatment, likelihood of referral for psychological assessment, or more frequent assessment for post-stroke depression. (97, 157) As a result, although current evidence is favourable regarding a relevant risk association between pre-stroke depression and post-stroke depression, we must remain cautious and changes to the approach for investigating this association are

needed. In particular, I would advise future studies seeking to assess risk factors for post-stroke depression to be aware of the potential care-pathway related confound and encourage greater consistency of depression assessment (both pre and post stroke).

Finally, I used two complementary approaches to inform my literature search, one specific search designed to find papers with a focus on pre-stroke depression and a more sensitive search with a post-stroke depression focus. Through various internal and external validity checks I believe I have captured all the relevant studies. However, it is possible that I may have missed prospective cohort studies with depression and stroke data where these variables are only available as secondary outcomes data and there have been no specific publications relating to depression and stroke.

4.4.4 Future Directions

My findings suggest avenues for further research. Optimal methods for assessing pre-stroke depression should be established, particularly as differences in assessment tool properties could interfere with correct identification of risk associations or result in improper patient care plans. Secondly, it would be beneficial to ascertain whether depression severity (e.g. major depression only vs “any depression”) is a source of variance for the risk of developing depression after stroke. Finally, the literature presents a clear correlation between pre-stroke depression and post-stroke depression; however, the specific aetiology of this association remains unknown. Previous studies have suggested that genetic factors may play a role.⁽⁵⁹⁾ The presence of particular psychological characteristics may also be relevant. For instance, selective attention towards negative attributes can lead to depression following disease (169) and is also a characteristic attributable to depression. Hence, a prior history of this cognitive style may increase the likelihood that this way of thinking will arise post-stroke, thus heightening risk of developing depression after stroke. Understanding the nature of the pre-stroke/post-stroke depression association should therefore help to tailor better treatment methods.

4.4.5 Clinical Implications

Stroke patients are at considerable risk of developing depression and having depression prior to the stroke event only serves to further heighten this risk. On this basis, it is important that clinicians are aware of the relevance of pre-stroke depression to the potential development of depression after a stroke, as well as the prevalence of the condition within their patient population (likely 1 in 6). Clinicians should also be aware of the potential limitations of relying upon medical records or patient self-reported diagnoses as means of identifying pre-stroke depression. It is likely that reliance upon such methods will fail to identify a substantial number of patients with the condition.

4.5 Conclusions

It seems clear from the existent literature that the prevalence of pre-stroke depression is strikingly lower than the depression prevalence observed after a stroke. Nevertheless, it appears that pre-stroke depression is an important and relevant clinical variable regarding the development of post-stroke depression. I would suggest that in those patients where pre-stroke depression is apparent, a high index of suspicion for post-stroke depression would be appropriate.

In a research context, efforts to investigate pre-stroke depression are currently hampered by the challenge of reliably assessing it: the most commonly employed methods utilised to detect pre-stroke depression are at risk of underestimating the prevalence of the condition. Utilisation of more thorough assessments of pre-stroke depression along with a careful consideration of relevant confounds and adequately powered statistical models are essential to the enablement of a more developed and nuanced understanding of pre-stroke depression and its relationship with post-stroke depression.

Chapter 5. Can informant tools be used to assess pre-stroke depression? An investigation of diagnostic test accuracy.

5.1 Introduction

Based on my findings in chapter 4, pre-stroke depression appears to exist in around 1 in 6 patients and its presence is associated with increased risk of post-stroke depression. However, assessment method employed contributes variance and there does not appear to be an agreed upon optimal method for assessing pre-stroke depression. Of the 5 different methods utilised in the studies included in my review, clinical interviews are likely the most robust method, but they are not suitable for routine use in busy acute stroke units. Medical records were the most commonly adopted method to identify pre-stroke depression; however, the differential prevalence rates observed suggest that medical records lack sensitivity to pre-stroke depression. There is a need, therefore, to identify methods more suited to routine pre-stroke depression assessment.

There are a large number of brief patient self-report depression screening assessments available; (see Figure 5-1) however, their use in stroke is limited by confounding conditions such as aphasia, cognitive impairment, and delirium.

(170)

Figure 5-1: Common Depression assessment tools

Geriatric depression scale (GDS)
Hospital anxiety and depression scale (HADS)
Patient Health Questionnaire (PHQ)
Signs of Depression Scale (SoDS)
Visual Analogue Mood Scales (VAMS)
Yale Single Question
General Health Questionnaire (GHQ)
Center for Epidemiologic Studies Depression Scale (CESD)
Brief Assessment Schedule Depression Cards (BASDEC)
Beck Depression Inventory (BDI)
Aphasia Depression Rating Scale (ADRS)

Informant assessments may be a viable and inclusive alternative. This approach is widely utilised in stroke to assess pre-stroke cognitive impairment but is not typically employed to assess pre-stroke mood. In contrast to cognitive assessment, specific informant questionnaires for assessment of depression *in stroke* have been developed, such as the Stroke Aphasic Depression Questionnaire (SADQ). (171) Twenty-one-item and 10-item versions of the scale exist, as well as a hospital-specific variation (SADQH-10). Reported sensitivity and specificity for detection of depression ranges from 70-100 and 69-81, respectively. (172) Additional psychometric properties are also favourable: the tool takes just 4 mins to complete, supporting feasibility; it has good test-retest reliability, and internal consistency; while concurrent validity is supported based upon strong correlations with other measures of depression. (173-175) A recent review(172) identified the SADQ as the only tool to meet psychometric and clinical criteria for assessment of ‘any depression’ in stroke.

Alternatively, the Geriatric Depression Scale (GDS) (176) is a commonly used depression screening tool designed specifically for use in older adult populations; (170) it was recently identified as a suitable direct-to-patient

depression screening tool for use in stroke. (172) A short-form informant version (GDS-SF) of the tool is freely available (177) and takes ~5 minutes to complete. (172) Moreover, the GDS-SF has demonstrated sensitivity >80% and specificity >60% for depression assessment in stroke. (172)

As both the SADQ and the GDS were designed to assess ongoing mood, it is unclear if this validity translates to evaluating premorbid mood as is necessary for pre-stroke depression assessment. I therefore aimed to investigate and compare the diagnostic test accuracy of the SADQ-H10 and an informant version of the GDS-SF as a means of assessing pre-stroke depression in an acute stroke setting. As a secondary aim, I sought to compare this diagnostic test accuracy against that of the more commonly employed method of pre-stroke depression assessment—patient medical records.

5.1.1 Hypothesis

For my primary aim, I hypothesized that the informant assessment approach would be a valid method for assessment of pre-stroke depression, with both tools performing significantly above chance level when discriminating between (pre-stroke) depressed and non-depressed patients.

For my secondary aim, I hypothesised that the informant method would demonstrate significantly superior sensitivity to patient medical records when assessing pre-stroke depression.

5.2 Method

This study utilised the same participant pool, design and inclusion/exclusion criteria as that described in chapter 3, section 3.2. Details of assessment are described below.

5.2.1 Informant tool assessment

Each participant's informant was asked to complete the SADQ-H10 and GDS-SF, which were administered in alternating order from patient to patient, by stroke research nurses trained in administration of the questionnaires. The SADQ-H10 involved 10 questions related to mood in the previous week and operates according to a 4-point Likert scale (not at all this week, 1-4 days this week, 4-6 days this week, every day this week). Items are scored from 0-3 and totalled out of 30. A score of >5 suggests depression is present. The GDS-SF involves 15 questions related to mood and each question is scored according to a binary scale (yes/no; plus, a 'don't know' option). Scores for each question are totalled to give a score out of 15. A score of >5 suggests depression is present. (see Appendices 11 and 12)

Informants were asked to complete the questionnaires in relation to how the patient's mood was before their most recent stroke occurrence. Time-frame for completion was within 1 month following admission; however, this requirement was relaxed towards the end of the study to assist recruitment. Questionnaires could be completed in the presence of the consenting researcher while the patient was still in hospital; or, if necessary, alone following patient discharge and returned via post.

5.2.2 Gold standard assessment

Major and minor depression were diagnosed according to DSM-5 criteria. (30)

Presence of a pre-stroke (major or minor) depressive episode was determined for each patient, via a clinical interview with the patient and/or the informant. All interviews were conducted utilising the Structured Clinical Interview for Depression (SCID) by a researcher (MT) trained in use of the SCID and blinded to results of the informant questionnaires. As informant tools are designed to screen for evidence of present low mood, rather than a history of low mood, the time-frame examined within the clinical interview for prior depressive episode occurrence was limited to the 6 months before the stroke; depressive episodes at any point in the life-time was not assessed via gold standard interview.

Interviews were conducted either face-to-face (preferentially) or via telephone (where necessary). As with the informant questionnaires, the SCID interview was initially required to be completed within 1 month following patient hospital admission for the stroke; however, this requirement was relaxed towards the end of the study. Following SCID interview, a consensus diagnosis was reached via discussion between the interviewing researcher (MT) and a stroke consultant (TQ). In contrast to the gold standard assessment process described in chapter 3, section 3.2, we did not adopt any means of establishing a diagnosis of ongoing pre-stroke depression if the SCID was not completed; hence, if both the patient or the patient's informant could not participate in the SCID assessment, the gold standard diagnosis could not be established for this patient.

5.2.3 Assessment of pre-stroke depression via medical records

As I was interested in the comparative diagnostic test accuracy performance of informant questionnaires to that of medical records for assessment of pre-stroke depressive episodes, patient medical records were also examined to identify pre-stroke depression. Patients were considered to have a recent pre-stroke depressive episode if they had a prior diagnosis of major/minor depressive disorder and were taking an anti-depressant drug in the 6 months before the stroke. Anti-depressant drugs used in the UK were identified on the British National Formulary. The specific drugs searched for can be seen in Table 5-1.

Table 5-1. Anti-depressant drugs searched for on the British National Formulary

Drug name	
Amitriptyline hydrochloride	Sertraline
Clomipramine hydrochloride	Tranlycypromine
Dosulepin hydrochloride	Trazodone hydrochloride
Doxepin	Trimipramine
Duloxetine	Venlafaxine
Escitalopram	Vortioxetine
Imipramine hydrochloride	Sertraline
Isocarboxazid	Paroxetine
Lofepamine	Fluoxetine
Mianserin hydrochloride	Citalopram
Mirtazapine	Venlafaxine
Moclobemide	Escitalopram
Nortriptyline	Paroxetine
Reboxetine	

5.2.4 Clinical and demographic data

Patient level data was collected via a combination of medical records or patient self-report. Stroke severity was assessed via NIHSS using retrospective chart review. (130) Pre-stroke disability was assessed via the pre-stroke modified Rankin Scale (pre-stroke mRS). Pre-stroke cognitive impairment was assessed via the method described in chapter 3 section 3.2.

5.2.5 Statistical analysis

MedCalc version 18.11 was used for all analyses. I adopted a 2-stage approach to analysis.

5.2.5.1 Stage1

In the first stage, performance of informant tools were evaluated against the gold standard assessment diagnosis. The Area Under the Receiver Operating Characteristic (AUROC) curve for each informant tool was determined via empirical Receiver Operating Characteristic (ROC) curves using the Delong et al., (1988)(132) method and compared using Pairwise comparisons. Next, I established the sensitivity and specificity, along with associated 95% confidence intervals, of the two informant tools for detecting a prior depressive episode at commonly used cut-points via 2x2 tables. I then compared the sensitivity and specificity values of each tool statistically when there were >20 cases for comparison, using McNemar's test. Following this, I investigated if the recommended published cut-points (>5) were the optimal cut-points for assessing pre-stroke depression within our population, based on the point nearest the top left-hand corner of the ROC graph. (81) Where an alternate cut-point was suggested, I repeated the analysis to evaluate sensitivity and specificity at optimal cut-points.

Where data was missing, I applied the average score of the answered questions to the unanswered question/s on the SADQ-H10, provided no more than 2 questions were unanswered. For the GDS-SF, I scored missing responses as 'no' responses. If more than two questions were unanswered for either tool, the

questionnaire data was discarded. 'Don't know' responses for the GDS-SF were also treated as 'no' responses for scoring purposes.

Stage 1 sensitivity analysis

I conducted a series of sensitivity analysis to explore potential influences upon my results by altering data then rerunning analysis in the following ways:

To ensure that any differences in informant tool diagnostic test accuracy properties were not overly influenced by assessment order, I sub-grouped the informant tools by order of administration and compared resultant sensitivity and specificity values of the two groups.

I ran a sensitivity analysis to determine if results changed based on scoring 'don't know' /missing responses as a 'yes'.

I investigated the influence of time-frame on diagnostic test accuracy by removing cases where completion of informant questionnaires or gold-standard was >31 days following stroke.

5.2.5.2 Stage 2

Based upon diagnostic test accuracy performance of the two tools in stage 1, for the stage 2 analysis I selected the best performing tool and evaluated the relative performance of the selected informant tool against that of medical records (dichotomised as depression present/depression not present) for assessing pre-stroke depression, again using the SCID diagnosis as the gold standard comparator for both methods. I generated sensitivity and specificity scores for medical records using 2x2 tables, then used McNemar's test to compare these values against those of the chosen informant tool when employed at its recommended published cut-point (>5).

When selecting the best performing tool, priority was given to the tools' respective performance at their most commonly used recommended cut-point, and a greater emphasis was placed on sensitivity of the tools, over specificity.

5.3 Results

5.3.1 Stage 1: Comparison of SADQ and GDS-SF informant

The population numbers were as described in chapter 3; however, 2 additional patients were assessed between 1st Dec 2018 and 31st Dec 2018 so were added to the population. Six patients described in chapter 3 as being unable to participate in the clinical interview were excluded from analysis of this study. This left a total of 91 patients with informants for diagnostic test accuracy evaluation of the SADQ-H10 and GDS-SF. Seventy out of 91 (77%) patients included in analysis in this study were recruited from the Glasgow Royal Infirmary.

There was missing data for the SADQ-H10 in 3/91 (4%) patients; missing data in 1/90 (1%) was too extensive such that the data could not be utilised. Missing data was present for 10/91 (11%) GDS-SF's; the missing data was substantial in 2/91 (2%) and so could not be utilised. This left SADQ-H10 data available for 90 patients and GDS-SF assessments available for 89 patients. The GDS-SF contained 'don't know' responses in 36/91 (40%) forms. Median time for completion of informant assessment following admission was 5 days; Median time for completion of gold standard assessment following admission was 7 days. A total of 18 patients were depressed before their stroke (13 major depressive episodes, 5 minor depressive episodes) according to 'gold standard' diagnosis. Population descriptive statistics can be seen in Table 5-2.

Table 5-2: Population Descriptive Statistics

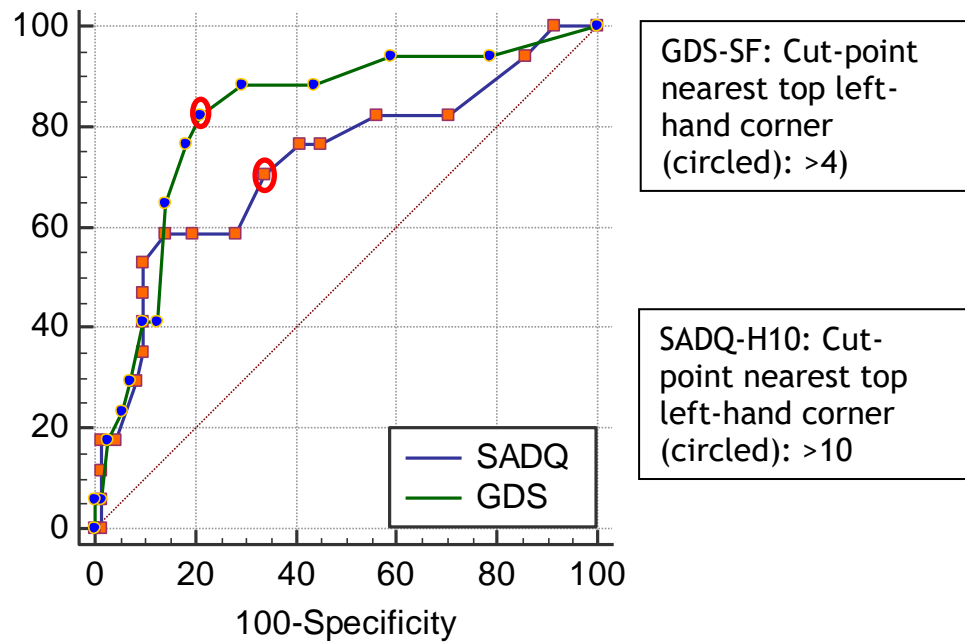
Variable	Overall
Age (Median; 25th-75th Percentile)	73 (61-80)
Sex Male (%)	46/84 (54.8%)
Stroke-type (%)	
<i>Total Anterior Circulation Stroke</i>	6/77 (7.8%)
<i>Partial Anterior Circulation Stroke</i>	25/77 (32.4%)
<i>Lacunar Stroke</i>	9/77 (11.7%)
<i>Posterior Circulation Stroke</i>	21/77 (27.3%)
<i>Trans Ischaemic Attack</i>	16/77 (20.8%)
NIHSS (Median; IQR)	1 (0-4)
Pre-stroke modified Rankin Scale (nn; %)	
0	31/81 (32.0%)
1	14/81 (14.4%)
2	13/81 (13.4%)
3	18/81 (18.6%)
4	5/81 (5.2%)
Pre-stroke cognitive disorder (nn; %)	27/91 (29.7%)
Post-stroke Aphasia (nn; %)	4/84 (4.1%)
Previous stroke	22/81 (27.2%)
Diabetes	15/76 (15.5%)
Atrial Fibrillation	14/76 (14.4%)
Medication count (Median; 25th-75thPercentile)	7 (5-10)

AUROC curve was 0.71 (95%CI=0.60-0.80), $p < 0.01$, for the SADQ-H10 and 0.82 (95%CI= 0.73-0.90), $p < 0.01$, for the GDS-SF. Pairwise comparison of AUROC curves suggested there was no statistically significant difference between the two tools (Difference between areas=0.09, 95%CI=-0.05-0.23; $p = 0.19$). A post-hoc power calculation was conducted to determine if pairwise comparison was underpowered to detect a 0.10 difference in AUROC, with 0.8 power and a 20% condition prevalence. Results suggested that 366 patients would be needed to determine if the observed difference was statistically significant at $p < 0.05$.

At cut-point >5 , sensitivity for the SADQ-H10 for detecting any depressive episode in the preceding 6 months before the stroke was 72.2% (95%CI=46.5%-90.3%); specificity was 62.7% (95%CI=50.3%-73.6%). Sensitivity of the GDS-SF for depression at a cut-point of >5 was 76.5% (95%CI=50.1%-93.2%); specificity was 84.7% (95%CI=74.3%-92.1%). A total of 88 patients had both SADQ-H10 and GDS-SF data available for statistical comparison of sensitivity and specificity rates. There were insufficient numbers with depression [18] to compare sensitivity rates statistically; however, McNemar's test for a difference in specificity suggested the GDS-SF had significantly better specificity than the SADQ-H10 (Difference: 22.2%; 95%CI=11.9%-32.6%), $p < 0.01$.

Empirical ROC curves suggested that the recommended published cut-point for the tools were not the optimal cut-point (see Figure 5-2). I therefore repeated the analysis, applying a cut-point of >10 for the SADQ-H10 and >4 for the GDS-SF. Sensitivity for the SADQ-H10 was 55.6% (95%CI=30.8%-78.5%); specificity was 86.1% (95%CI=75.9%-93.1%). For the GDS-SF, sensitivity was 82.4% (95%CI=56.6%-96.2%); specificity was 79.2% (95%CI=68.0%-87.8%). McNemar's test for specificity suggested no significant difference between the 2 tools (Difference:-7.0%; 95%CI= -16.1%-1.9%), $p = 0.23$.

Figure 5-2. Combined ROC curves for SADQ-H10 and GDS-SF



5.3.1.1 Sensitivity analysis

SADQ-H10 was administered first with 41 participants (10 cases of gold standard defined depression); GDS-SF administered first with 50 participants (8 cases of gold standard defined depression). Sensitivity analysis based on order of administration showed that when administered first, at recommended published cut-points, GDS-SF sensitivity was 85.7% (95%CI=42.1% to 99.6%), specificity was 85.7% (95%CI=71.5%-94.6%); AUROC for GDS when administered first was 0.94 (95%CI=0.84-0.99), $p < 0.01$. When SADQ-H10 was administered second, sensitivity was 87.5% (95%CI=47.4%-99.7%), and specificity was 61.9% (95%CI=45.6%-76.4%); AUROC for SADQ-H10 when administered second was 0.81 (95%CI=0.68-0.91), $p < 0.01$. When administered second, GDS-SF sensitivity was 70.0% (95%CI=34.8%-93.3%), specificity was 68.9% (95%CI=49.2%-84.7%); AUROC for GDS-SF when administered second was 0.69 (95%CI=0.52-0.82), $p = 0.06$. When administered first, SADQ-H10 sensitivity was 60.0% (95%CI=26.2%-87.8%), specificity was 56.7% (95%CI=37.4%-74.5%). AUROC when SADQ-H10 was administered first was 0.63 (95%CI=0.46-0.78), $p = 0.27$.

I evaluated if scoring GDS-SF 'don't know' /missing responses as 'yes' altered sensitivity and specificity rates at recommended published cut-points.

Sensitivity of GDS-SF did not change (76.5%, 95%CI=50.1%-93.2%); however, specificity was slightly reduced when adopting this method (73.6%, 95%CI=61.9%-83.3%). AUROC curve was 0.80 (95%CI=0.71-0.88), $p < 0.01$.

I removed 12 cases in which the informant questionnaire and/or gold standard assessment was completed >31 days following hospital admission for stroke. Results suggest inclusion of these cases did not substantially influence test accuracy. Sensitivity and specificity rates at recommended published cut-points were: SADQ-H10 sensitivity=73.3% (95%CI=44.9%-92.2%), specificity=65.1% (95%CI=52.0%-76.7%), AUROC=0.73 (95%CI=0.61-0.82), $p < 0.01$; GDS-SF sensitivity=71.4% (95%CI= 41.9%-91.6%), specificity=87.3% (95%CI=76.5%-94.4%), AUROC curve=0.84 (95%CI=0.734-0.911), $p < 0.01$.

5.3.2 Stage 2: Comparison with medical records

Based upon the above properties, the GDS-SF was selected for comparison against the use of medical records to detect depression in the 6 months before the stroke. Medical information was available for all 89 patients with GDS-SF data.

Sensitivity of medical records to detection of depressive episodes in the 6 months preceding the stroke was 50.0% (95%CI=26.0%-74.0%); specificity was 81.9% (95%CI=71.1%-90.0%).

There was insufficient data to compare sensitivity values of the GDS-SF and medical records statistically; McNemar's test of specificity values at both recommended and optimal cut-points suggested no significant difference (Size difference: 2.8%; $p=1.00$) between the two methods.

Additional diagnostic test accuracy properties for both informant tools at their recommended published cut-points (>5) along with use of medical records can be seen in Table 5-3.

Table 5-3: Properties of 3 assessment methods

	SADQ-H10	GDS-SF	Medical records
Positive likelihood ratio	1.79 (95%CI=1.20 to 2.68)	5.01(95%CI= 2.73 to 9.16)	2.77 (95%CI= 1.41 to 5.44)
Negative likelihood ratio	0.47(95%CI=0.22 to 1.00)	0.28 (95%CI=0.12 to 0.66)	0.61 (95%CI= 0.38 to 0.98)
Positive predictive value	30.9% (95%CI=23.1% to 40.1%)	54.2% (95%CI=39.2% to 68.4%)	40.9% (95%CI= 26.1% to 57.6%)
Negative predictive value	89.6% (95%CI=79.9% to 94.9%)	93.9% (95%CI=86.6% to 97.3%)	86.8% (95%CI= 80.3% to 91.3%)
Prevalence (pre-stroke depression)	20.0% (95%CI=12.3% to 29.6%)	19.1% (95%CI=11.5% to 28.8%)	20.0% (95%CI= 12.3% to 29.8%)

5.4 Discussion

5.4.1 Informant tool comparative diagnostic test accuracy

On the surface, my results offer preliminary support regarding the validity of informant tools as a method for assessing pre-stroke depression. As hypothesised, both tools' overall diagnostic test accuracy performance (AUROC) was significantly above chance level, suggesting the SADQ-H10 and GDS-SF informant tools are a valid means of assessing pre-stroke depression. The AUROC of the two tools differed by ~10% in favour of the GDS-SF and suggest the GDS-SF has 'good' (0.80-0.89) discriminability between patients with pre-stroke depression and those with no pre-stroke depression, while the SADQ-H10 has 'fair' (0.70-0.79) discriminability. However, this difference was not statistically significant. It is likely that the lack of statistical significance is related to the lack of power in my study sample. Regardless, future studies are required to confirm if indeed the GDS-SF has an overall superior diagnostic test accuracy for pre-stroke depression than the SADQ-H10.

Comparative performance of the tools at most commonly applied recommended cut-points also favoured the GDS-SF over the SADQ-H10. The GDS-SF demonstrated significantly fewer false positive diagnoses than the SADQ-H10 and while I could not statistically compare sensitivity values, the presenting rates were highly similar. This increased specificity suggests the GDS-SF offers an important clinical advantage over the SADQ-H10. Utilisation of this tool may minimise the number of patients misidentified as having had a pre-stroke depressive episode.

To my knowledge, there is no prior research on the diagnostic test accuracy properties of these tools for assessment of pre-stroke depression. The observed sensitivity and specificity values are however broadly consistent with previous findings regarding tool validity when used to assess post-stroke depression. At cut-point >5, the SADQ-H10 has reported sensitivity rates ranging from 70-100% and specificity ranging from 69-78%. (174, 178) However, this performance is described in studies that employed other depression screening tools as the reference standard; (172) as such, they arguably do not reflect the tool's ability

to assess depression *per se*, but rather, depressive symptoms. My findings therefore add to the SADQ-H10 validity literature, suggesting the SADQ-H10 can discriminate between stroke patients with and without DSM-5 defined major and minor depression—albeit in a pre-stroke context. I would note, however, that while my findings suggest the SADQ-H10 can discriminate such patients, its overall performance for this purpose is relatively weak, consistent with Leeds et al., (2004)(173) who question the tool’s validity when utilised with non-aphasic patients.

The diagnostic test accuracy of the GDS-SF has previously been questioned. (86) Roger and Johnson-Greene (2009)(179) reported a GDS-SF sensitivity of just 46% for DSM-IV defined major or minor depression when utilised in a stroke rehabilitation population. My results support the use of the GDS-SF as a tool capable of detecting cases of depression and are more consistent with the findings of Lee et al., (2008)(180), who report a GDS-SF sensitivity rate of 84%; though, as a caveat, our lower bound confidence intervals suggest GDS-SF sensitivity could be as low as 50%, thus more research is required to establish the GDS-SF sensitivity values in general.

Alternate cut-points for both tools may be more suited to assessment of pre-stroke depression than the recommended published cut-points. Indeed, it is possible that the differences in specificity between the tools could be allayed by application of a higher, optimal, cut-point for the SADQ-H10. However, altering the cut-point may come at a substantial cost to the sensitivity of the SADQ-H10. In relation, Meader et al., (2013)(86) suggest that the GDS-SF has substantial heterogeneity of use in the literature already, leading to notable variation in comparative performance; therefore, as discussed in chapter 3, section 3.4, I do not recommend that researchers and clinicians stray from the published cut-points until further work is conducted.

5.4.2 Comparison with medical records

Despite being the most commonly utilised method to detect pre-stroke depression in the studies that were included in my systematic review, medical records may be a suboptimal means of assessment. I hypothesised that our

chosen informant tool would be significantly more sensitive to pre-stroke depression than medical records. My results are inconclusive in relation to this hypothesis due to a lack of statistical power; however, they are suggestive that medical records may lack sensitivity regarding ongoing pre-stroke depressive episodes, consistent with the results in chapter 4.

Nevertheless, I would acknowledge that, while it is possible that medical records have a tendency to miss cases of ongoing pre-stroke depression, the observed specificity values were good and comparable to the GDS-SF. Moreover, medical records are capable of identifying patients that do not exhibit ongoing (pre-stroke) depressed mood, but who have a prior, historic diagnosis of depression. In the current evidence base, it is not clear that a previous, but dormant, history of depression is any less of a risk factor for post-stroke depression than recent (e.g. prior 6 months), or ongoing depressive episodes. (97, 142, 164) Hence, such patients are likely also of clinical relevance. I therefore do not envisage any circumstance where informant tools should be utilised as a replacement for medical records when screening for pre-stroke depression, but rather they could be a helpful supplement. A larger study is necessary to confirm these speculations.

5.4.3 Strengths and limitations

I have conducted an inclusive study, following best guidelines for evaluating tool diagnostic test accuracy. However, there are some important limitations to our study beyond those described in chapter 3, section 3.4.3.

Most prominent is the lack of statistical power—a consequence of the limited patient numbers with depression in my sample. This restricted the precision with which I could report the sensitivity rates of the respective assessment methods and prohibited any formal statistical sensitivity comparisons between the tools.

Assessment order may have influenced overall diagnostic test accuracy evaluation as both tools' diagnostic properties appear to have been influenced by this. In fact, when the SADQ-H10 was administered first and the GDS-SF

second, I failed to find evidence that either tool performed statistically significantly above chance level (AUROC was not statistically significantly above 0.5). This poses serious questions regarding both tools' general validity as measures of pre-stroke depression and limits the certainty of the statistically significant results we report in our primary analysis. It is unclear why administration order would alter test accuracy to this extent and the result may be simply be a product of the reduced power in this particular analysis (only 41 cases). Regardless, this warrants further investigation and the possibility justifies incorporation of alternating administration order into this study's design.

In addition, the SADQ-H10 is designed to be administered 2 times for each patient with scores >5 for 2 consecutive weeks indicating depression. In this study, informants were only required to complete the SADQ-H10 once; hence this tool was utilised in an unconventional way, beyond simply adopting a retrospective approach to assessment.

Finally, the gold standard assessment was imperfect. As in chapter 3, informants contributed to both questionnaire and interview-based assessment methods and it is unclear how much this may have biased diagnostic test accuracy results. While informant assessment of cognition is often shown to be more reliable than patient self-report (181), it is less clear if this is also true of mood assessment in stroke. There is therefore a particular potential for bias in patients with post-stroke aphasia where only the informant was able to take part in clinical interview. Moreover, employing a retrospective approach to gold standard assessment whereby patients/informants were asked to recall mood in the 6 months leading up to the stroke is vulnerable to recall bias; and patients with pre-stroke cognitive or physical problems may experience mood issues differently to those without (182), which may have confounded the SCID interview in these cases.

5.4.4 Clinical implications

It is yet to be established if pre-stroke depression assessment is a clinically beneficial practice. In theory, it could support tackling the burden of post-stroke depression.

Post-stroke depression is prevalent (59) but often undiagnosed and inadequately treated; (68) therefore, post-stroke mood screening is recommended. (183, 184) However, recognition can be confounded by somatic issues that may be symptoms of the stroke or a consequence of hospital admission (e.g. fatigue, aches and pains, altered sleep).(185) Some mood screening tools do not adopt somatic items for this reason (186-188) but most depression tools incorporate somatic items into their assessment (176, 189-191) and there is evidence that somatic items are among the best differentiators between stroke patients with and without depression. (192)

Incorporation of a pre-stroke depression assessment to post-stroke mood screening may help to establish those patients who exhibited somatic symptoms before the stroke and hence help differentiate from patients only experiencing such symptoms post-stroke, potentially aiding depression diagnostic accuracy. It could also elucidate those most likely to exhibit depression following stroke, highlighting patients suitable for preventative treatment—albeit this must be tempered with the potential risks of administering anti-depressant treatment in stroke.(193) As typical barriers to mood screening include lack of knowledge and consensus for tool selection (194), my results should assist appropriate adoption of pre-stroke depression assessment in the acute stroke setting, if indeed this is established as a viable and useful practice.

5.4.5 Future studies

Validity is only one component in the makeup of the psychometric properties of pre-stroke depression informant questionnaires; feasibility, acceptability and reliability are also relevant. (78)

I offer some limited data on feasibility which suggests that, while missing data is relatively common (particularly in the GDS-SF), these questionnaires can still be completed in the vast majority of patients who have an informant available. However, acceptability may be compromised: almost half of GDS-SF assessments contained 'don't know' responses, suggesting informants may struggle with evaluating a person's pre-stroke mood, generally. On this basis, adopting an informant approach to pre-stroke mood assessment may only be preferable when patient self-report assessment is not possible or deeply limited due to confusion or aphasia. Further work on the optimal method, wider psychometric properties, and benefits of pre-stroke depression assessment are required to clarify these outstanding queries.

5.5 Conclusions

In conclusion, informant tools appear to be a valid measure of assessing recent pre-stroke depression, albeit my data are limited by low power and some potential sources of bias and confounding that must be clarified before any firm conclusions can be made. There is preliminary evidence that the GDS-SF may have greater diagnostic test accuracy for pre-stroke depression assessment than the SADQ-H10; but also, that the most commonly applied cut-points may not be optimal. Consistent with my findings in chapter 4, medical records appear to miss cases of pre-stroke depression. While I could not confirm statistically that the GDS-SF offers greater sensitivity, the substantial difference in sensitivity rates indicates that this may be the case. This is a promising avenue for further research into pre-stroke depression assessment but requires a larger study sample for confirmation. On the basis of our study limitations, I cannot draw any firm conclusions regarding the use of informant tools for assessment of pre-stroke depression and encourage further research into this area.

Chapter 6. Pre-stroke modified Rankin Scale: evaluation of validity, prognostic accuracy and association with treatment.

6.1 Introduction

As well as clinical utility, robust measures of pre-stroke function are needed for psychological research. Dementia diagnosis requires identification of problems in both cognition and everyday functioning. As discussed in chapter 2, section 2.3, pre-stroke functioning has been associated with post-stroke dementia risk, hence measuring pre-stroke function has relevance to understanding psychological problems in stroke; however, its importance stretches beyond this. It is often employed as exclusion criterion or case mix adjuster for trials and international registries. (102, 195) This approach recognises that even the best treatment is unlikely to improve function to better than the pre-stroke state. Pre-stroke disability may also have important prognostic utility, although data on this have been conflicting. (89, 109)

While the need to describe pre-stroke function is apparent, the method of achieving this is less certain. The modified Rankin scale (mRS) is a measure of global disability that is commonly used as a functional outcome for stroke studies, (196) and has also been used to evaluate pre-stroke disability levels, (197). Pre-stroke mRS has been used extensively in research, audit and service planning. (102, 195, 198). In practice, decisions on treatment are often based on premorbid function. (199)

Use of pre-stroke mRS for these purposes is potentially problematic as the clinical properties of the pre-stroke mRS have not been as thoroughly investigated as traditional post-stroke mRS, (200). While validation studies of pre-stroke mRS exist, (89) limited sample sizes leave questions around generalisability, and it is unclear to what extent reported predictive validity may be driven by differences in care-pathway. (109)

There is therefore a need for further validation work on the pre-stroke mRS and, based on the current usage of pre-stroke mRS, key questions emerge: If pre-stroke mRS is used to assess prevalent disability, is it a valid measure of this construct? If pre-stroke disability is used as a component item in prognostic models, what is the independent contribution of pre-stroke mRS to outcome? If pre-stroke mRS is associated with outcome, can this be explained by differing process of care?

In this study, my collaborators and I aimed to use UK multicentre, clinical cohort to answer the above important and relevant research questions. Therefore, the specific aims of this study were:

- 1) To assess the 'validity' of pre-stroke mRS by comparison with other related disability metrics.
- 2) To assess association of pre-stroke mRS with short and longer term mortality prognosis in a 'real world' sample.
- 3) To assess if pre-stroke mRS is associated with a differing process of care.

6.2 Methods

6.2.1 Population

We used the data held in the Anglia Stroke Clinical Network Evaluation Study (ASCNES). ASCNES was a multi-centre, prospective cohort study. ASCNES collected clinical data from sequential stroke admissions across 8 acute NHS (National Health Service) trusts in the East of England, UK (Norfolk, Suffolk, and Cambridgeshire). Data collection was from October 2009 to September 2011 inclusive. Data capture included a 1 year follow-up.

The full details of ASCNES have been described previously. (201) In brief, included patients were aged over 18 years, with stroke confirmed and

phenotyped by expert multidisciplinary clinical assessment. Our population included both first ever stroke and recurrent stroke and all included patients were treated as per institutional practice and stroke guidelines. Relevant institutional and ethical approvals for use of these data were in place.

6.2.2 MRS assessment

The ASCNES dataset was based on the modification of the Basic European Stroke Register Database but including process of care measures. Data were collected by clinical staff and transferred to an electronic database. Pre-stroke mRS was part of the initial assessment. All mRS assessments (pre and post-stroke) were performed by clinical staff using an unstructured interview and based on history taken from patient whenever possible, or their significant others/carers. The participating sites offered no explicit guidance on applying mRS grades as a pre-stroke measure and final score was at the discretion of the assessor. (see Appendix 13)

6.2.3 Analyses

We used basic descriptive statistics to describe baseline variables of included patients. As pre-stroke mRS was a key variable we compared those with and without pre-stroke mRS against pre-specified variables of age, sex, NIHSS, stroke type (ischaemic or haemorrhagic), systolic blood pressure (BP), atrial fibrillation (AF), blood glucose and Oxford Community Stroke Project (OCSP) classification.

6.2.3.1 Validity of pre-stroke mRS

We described concurrent validity of pre-stroke mRS by comparison with other baseline clinical and demographic variables that are known to be associated with physical function. Our chosen comparators were, age, co-morbidity burden assessed by Charlson comorbidity index, (202), mRS at discharge, pre-stroke residence (categorised as: Home, Sheltered housing, Rehabilitation Centre, Care home) and receipt of formal care pre-stroke (categorised as: lives alone, lives with family, external carers, sheltered housing, institutional care).

We described association of pre-stroke mRS with other variables using chi-square for proportional data and Spearman rank correlation for nominal data. We re-categorised pre-stroke residence as “own home” or other (comprising any form of institutional care) and calculated odds-ratios for each pre-stroke mRS grade.

6.2.3.2 Association of pre-stroke mRS and outcomes

We examined the association between pre-stroke mRS and selected outcomes which included mortality at 7 days and 1 year; length of stay (days); discharge destination (categorised as per our validity analyses) and post-stroke complications of pneumonia and urinary tract infection. Due to modest numbers in pre-stroke mRS 4 and mRS 5, these categories were combined. We calculated univariable associations between pre-stroke mRS and outcomes of interest with strength of association described as odds ratio (OR) or beta for length of stay data. To compare pre-stroke mRS with other variables known to have prognostic importance we also described association with outcomes for age, sex, stroke type, modified early warning score (MEWS), glucose, AF and comorbidity. We then calculated OR for pre-stroke mRS adjusted for other important prognostic variables (NIHSS, age, sex).

6.2.3.3 Association of pre-stroke mRS and process of care

To describe association between pre-stroke mRS and process of care, we selected three aspects of acute stroke care that should be standard, are recommended in guidelines and have been shown to have utility regardless of pre-stroke function. Our chosen process of care markers were: assessment of swallow (in first 24 hours), (203); admission to dedicated stroke unit (SU) (days to SU admission from hospital admission and dichotomous yes/no), (204); brain imaging (days from admission to imaging and dichotomous yes/no), (205). Association of swallow test performed; admission to stroke unit and imaging performed with pre-stroke mRS was described for each factor using Mann-Whitney, association with categorised time to stroke unit admission (days) and time to imaging (days) was described using Cuzik test for trend.

6.2.3.4 Subgroup analyses

Recognising the difficulty in applying mRS to a population with no history of stroke we performed subgroup analyses, we described our validity and prognostic analyses comparing results for those with a previous history of stroke against first ever strokes. Recognising that the wording of the lower mRS grades make them more difficult to use as a pre-stroke assessment, we performed a further subgroup analysis comparing those with pre-stroke mRS 0-2 to those with pre-stroke mRS 3-5. Our dataset included patients admitted to University Teaching Hospitals and smaller 'General' Hospitals. Sites could plausibly assess pre-stroke mRS differently depending on training, exposure to research and staff mix. We tabulated pre-stroke mRS stratified by treating centre.

6.3 Results

A total of 2491 patients with stroke were included in the ASCNES dataset. The mean age was 76.4 years (SD, 13.1), 1311 (53%) were female; 2120 (85%) had ischaemic stroke. (Table 6-1)

Pre-stroke mRS data was available for 2001 patients. Median pre-stroke mRS was 0 (IQR, 0-2; range:0-5). Most frequent pre-stroke mRS score was 0. (Table 6-2) Pre-stroke mRS data were missing for 488 (24.4%) of the sample. There was no difference between those with and without mRS data for any of our pre-specified variables, other than OCSF where those with more severe strokes (TACS) were more likely to have missing pre-stroke mRS data (<0.05). Data was also missing for those with Atrial Fibrillation (AF) (308; 12.4%), Stroke type (51; 2%) and Bamford classification (334; 13.4%).

Table 6-1. Summary descriptive statistics of ASCNES data

Variable	N	Mean (SD) / median (IQR)	Min	Max
Age (years)	2487	76.4 (13.1)	18	101
Pre-stroke Rankin	2001	0 (0-2)	0(n=1027;51.3%)	5 (n=56; 2.7%)
MEWS [†]	2101	1.4 (1.3)	0	7
NIHSS [†]	673	7 (3-14)	0	36
Systolic BP (mmHg) [†]	2406	157.2 (30.5)	60	271
Glucose (mmol/l) [†]	2136	7.6 (3.0)	1.4	40.2
	N	%		
AF				
No	1469	59.0		
Yes	714	28.7		
Missing	308	12.4		
Stroke type				
ICH	320	12.9		
Infarct	2120	85.1		
Missing	51	2.0		
Bamford				
LACS	520	20.9		
PACS	856	34.4		
POCS	308	12.4		
TACS	473	19.0		
Missing	334	13.4		
Sex				
Female	1311	52.6		
Male	1178	47.3		

MEWS= Modified Early Warning Score (scale of 0-6+; higher scores indicate greater concern for health based on cardinal vital signs; 1-3=low concern; 4 or 5=medium concern; 6+=high concern); NIHSS= National Institute of Health Stroke Scale; BP=Blood Pressure; AF= Atrial Fibrillation; ICH= Intracerebral haemorrhage; [†]measured on admission.

Table 6-2. Frequency of pre-stroke mRS score

Pre-stroke mRS rating	Score frequency (%)
mRS 0	1027 (51%)
mRS 1	367 (18%)
mRS 2	207 (10%)
mRS 3	212 (11%)
mRS 4	132 (7%)
mRS 5	56 (3%)

mRS= modified Rankin Scale

6.3.1 Validity of pre-stroke mRS

Of included patients, 1240 (49.8%) were living alone with no carers prior to admission. Median Charlson comorbidity index was 5 (IQR, 4-6). Age at time of stroke, discharge mRS, pre-stroke residence, pre-stroke care and Charlson comorbidity index were all associated with pre-stroke mRS ($\rho > 0.40$ for continuous variables, $P < 0.0001$). (Table 6-3)

Every point increase in pre-stroke mRS was associated with an increased association of living in institutional care pre-stroke. For example, comparing pre-stroke mRS 0 and 5, odds ratio (OR) of institutional care pre-stroke was 73 (95% Confidence Interval [95%CI]:37-143).

On our subgroup analyses looking at those with previous stroke and those with lower pre-stroke mRS values, there was no clear and consistent difference between groups. (Table 6-4)

Inspection of pre-stroke mRS classification by treating centre suggested differential scoring at lower mRS grades between sites. The large number of sites and modest number of participants in certain grades precluded formal comparative analyses. (Table 6-5)

Table 6-3. Association of Pre-stroke Rankin and other markers of function

Factor	Association	p-value
Age	0.40 (0.36,0.44) ¹	<0.0001
mRS on discharge	0.50 (0.46,0.53) ¹	<0.0001
Pre-stroke residence	995.5 ²	<0.0001
Pre-stroke formal care received	761.1 ²	<0.0001
Charlson co morbidity index	0.41 (0.37,0.44) ¹	<0.0001

¹ Spearman rank correlation coefficient (95% CI); ² Chi-squared test (Degrees of Freedom=9). mRS= modified Rankin Scale

Table 6-4. Association of Pre-stroke Rankin and other markers of function sub-grouped by previous stroke

	All	No Prev-stroke	Prev-stroke	mRS 0-2	mRS 3-5
Factor	Association				
Age	0.40 (0.36,0.44) ¹	0.42 (0.38,0.46)	0.24 (0.15,0.33)	0.30 (0.25,0.34)	0.00 *(- 0.09,0.10)
mRS on discharge	0.50 (0.46,0.53) ¹	0.47 (0.43,0.51)	0.54 (0.47,0.61)	0.32 (0.27,0.36)	0.34 (0.25,0.42)
Pre-stroke residence	995.5 ²	803.2	216.4	95.5	63.7
Pre-stroke formal care received	761.1 ²	649.0	145.2	181.8	40.9
Charlson comorbidity index	0.41 (0.37,0.44) ¹	0.40 (0.36,0.44)	0.21 (0.12,0.30)	0.33 (0.29,0.38)	0.06 *(- 0.04,0.16)

Table 6-5. Pre-stroke mRS scoring by centre contributing data

	Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6	Unit 7	Unit 8
mRS 0	99 (24.6)	5 (23.8)	128 (34.5)		368 (52.6)	148 (46.3)	153 (54.8)	126 (50.8)
mRS 1	68 (16.9)	5 (23.8)	76 (20.5)		97 (13.9)	17 (5.3)	65 (23.3)	39 (15.7)
mRS 2	26 (6.4)	4 (19.1)	55 (14.8)		61 (8.7)	17 (5.3)	20 (7.2)	24 (9.7)
mRS 3	24 (6.0)	2 (9.5)	39 (10.5)		76 (10.9)	22 (6.9)	16 (5.7)	33 (13.3)
mRS 4	9 (2.2)	4 (19.1)	39 (10.5)		38 (5.4)	12 (3.8)	10 (3.6)	20 (8.1)
mRS 5	0 (0.0)	1 (4.8)	8 (2.2)		26 (3.7)	9 (2.8)	6 (2.2)	6 (2.4)
Missing	176 (43.8)	0 (0.0)	26 (7.0)	150 (100)	34 (4.9)	95 (29.7)	9 (3.2)	0 (0.0)

Data are n (%) for each centre that contributed data to the database, unit 4 did not contribute pre-stroke mRS data.

6.3.2 Association of pre-stroke mRS and outcomes

Mean length of stay was 16 days (SD, 20). Discharge to home, with no carers was recorded in 689 (28%); 400 (16%) were transferred from acute hospital to a rehabilitation facility. One year mortality was 770 (31%); 7 day mortality 265 (11%). Of post-stroke complications, 288 (12%) developed pneumonia and 146 (6%) urinary tract infection. Every point increase in pre-stroke mRS was associated with greater numbers of poor outcomes for all our chosen outcomes. Strength of association was comparable to or higher than other known prognostic variables. Associations held when corrected for other covariates. For example, pre-stroke mRS score of 4 or 5 OR:6.84 (95%CI:4.24-11.03) compared to 0 in adjusted model. (See Appendices 14-19)

On our subgroup analyses looking at those with previous stroke and those with lower pre-stroke mRS values, there was no clear and consistent difference between groups. (Table 6-6.)

6.3.3 Pre-stroke mRS and processes of care

Of 2383 patients with relevant data, 1674 (70%) had a swallow test performed; 2287 (96%) had brain imaging, of whom 1520 (64%) were scanned within 24 hours; and 1886 (79%) were admitted to a stroke unit of whom 1162 (49%) were admitted on the same day. There was a difference in pre-stroke mRS between those who received swallow assessment ($p=0.04$) and brain imaging ($p=0.0003$) but not admission to ASU ($p=0.21$). This difference favoured those with greater disability i.e. higher pre-stroke mRS was more likely to receive these evidence based aspects of care. There was no apparent difference in time to stroke unit admission or imaging by pre-stroke mRS.

Table 6-6. Association between factors and death within 1 year (sub-grouped by previous stroke)

	No previous stroke				Previous stroke			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	1.08 (1.07, 1.09)	<0.001	1.04 (1.02,1 .06)	<0.01	1.06 (1.04,1 .09)	<0.001	1.05 (1.01,1 .09)	0.011
Male	0.61 (0.5,0. 74)	<0.001	0.77 (0.55,1 .07)	0.117	0.78 (0.55,1 .12)	0.187	0.87 (0.48,1 .56)	0.635
Pre-stroke Rankin		Trend:< 0.001		Trend:< 0.001		Trend:< 0.001		Trend:< 0.001
1 vs 0	1.96 (1.43, 2.69)		1.58 (1.03,2 .43)		3.15 (1.69,5 .85)		3.86 (1.62,9 .21)	
2 vs 0	2.74 (1.86, 4.05)		1.77 (1.06,2 .95)		2.82 (1.45,5 .48)		2.52 (1.06,5 .99)	
3 vs 0	5.82 (4.02, 8.43)		3.56 (2.12,5 .99)		4.48 (2.33,8 .65)		4.14 (1.79,9 .58)	
4 or 5 vs 0	12.72 (8.13, 19.9)		8.6 (4.61,1 6.04)		10.21 (5.31,1 9.64)		6.64 (2.81,1 5.67)	
ICH	2.32 (1.77, 3.03)	<0.001	3.75 (2.39,5 .89)	<0.01	2.2 (1.29,3 .76)	0.004	5.22 (2.27,1 1.98)	<0.01
MEW-S	1.32 (1.22, 1.43)	<0.001	1.18 (1.05,1 .33)	0.006	1.3 (1.13,1 .49)	<0.001	1.18 (0.97,1 .45)	0.104
Glucose	1.08 (1.04, 1.11)	<0.001	1.06 (1.01,1 .12)	0.027	1.06 (0.98,1 .14)	0.136	1.07 (0.97,1 .18)	0.173
AF	2.1 (1.69, 2.61)	<0.001	1.59 (1.14,2 .22)	0.007	1.88 (1.28,2 .77)	0.001	1.7 (0.97,2 .99)	0.065
Charlson index	1.39 (1.32, 1.46)	<0.001	1.19 (1.1,1. 3)	<0.01	1.28 (1.16,1 .41)	<0.001	1.15 (0.97,1 .36)	0.1

OR= Odds Ratio; AF= Atrial Fibrillation; MEWS= Modified Early Warning Score

6.4 Discussion

We sought to assess some of the key clinical properties of the pre-stroke mRS in order to address important questions as to its use in clinical research and practice. According to our results, the pre-stroke mRS has a validity that is close to what is considered as fair (<0.5) (206), albeit in the absence of a true gold standard for pre-stroke function these analyses are open to interpretation and the correlation described may be acceptable. Pre-stroke mRS is a potential tool for predicting prognostic outcome following stroke and the relationship between pre-stroke mRS scores and prognosis is not related to variations in patient care pathways.

Arguably the most important property of pre-stroke mRS is validity; the scale is of little utility if it does not measure what it purports to measure. We assessed concurrent validity and found that the pre-stroke mRS demonstrated significant, associations with all our chosen measures that should reflect pre-stroke disability. Although significant, the correlation we demonstrated was at best moderate in strength. This finding is similar to that of Fearon et al., (2012) (89) who found moderate correlations between pre-stroke mRS and pre-stroke comorbidity and frailty but not pre-stroke care needs. Although there are concerns that pre-stroke mRS may not be suited to first stroke events or those with good function pre-stroke, our subgroup analyses did not find any convincing evidence of this. Our results should reassure clinicians and researchers that pre-stroke mRS does capture pre-stroke function, but the moderate associations suggest there may be scope for further improvement.

Our results demonstrate that the pre-stroke mRS is a potential prognostic indicator. Although pre-stroke mRS is widely accepted to be an indicator of prognosis, there has been very little published work to confirm this. We found that as the pre-stroke mRS score increased, patients were more likely to experience negative outcomes and this pattern was consistent across all of our chosen outcome measures (LOS, discharge destination, mortality & complications after stroke). Furthermore, the strength of association of the pre-stroke mRS with each outcome variable was comparable or greater than that of

all of our other prognostic variables, suggesting that the prognostic utility of pre-stroke mRS is at least as strong as other commonly used indicators of prognosis. These findings are broadly consistent with those of Kwok et al., (2012)(109) who also found that pre-stroke mRS was a robust predictor of post-stroke outcome, as measured by mortality and length of stay. Our findings also extend the prognostic predictability of the pre-stroke mRS to that of eventual discharge destination and the prevalence of complications post-stroke.

Importantly, we also found that the association between pre-stroke mRS and outcome cannot be explained by differing process of care. Specifically, our results reveal that while there is a difference in the process of stroke care associated with pre-stroke mRS, this difference indicated that individuals who had higher pre-stroke mRS scores were *more* likely to be provided with access to evidence based stroke care. For instance, significantly more patients with higher pre-stroke disability scores received a swallow assessment and brain imaging; while there was no difference found in regards to pre-stroke mRS and time taken for admission to a stroke unit or for brain imaging. If anything, the pattern of care is likely to have reduced the association between pre-stroke mRS and outcome. It is therefore reassuring that the relationship between pre-stroke mRS and outcome appears to be based purely on the effect of premorbid disability on the overall impact of the stroke. Our data did not allow for more sophisticated analyses looking at hospital level confounders such as teaching hospital versus non-teaching hospital or staffing levels.

While our results suggest that the pre-stroke mRS has moderate validity as a tool for measuring pre-stroke function, more work is required on this property. Confidence in the ability of the pre-stroke mRS to detect premorbid disability is low and Bruno and Switzer (207) have gone as far as to say that the pre-stroke mRS is not fit for purpose in this regard. Future studies that focus on comparing the pre-stroke mRS with a more detailed assessment of pre-stroke function would help to resolve this question of validity.

Our study had a number of strengths. We had a large participant pool that allowed a multitude of comparisons between variables enabling revealing insights into the clinical properties of pre-stroke mRS. Our sample was also

taken from a 'real world' patient pool of consecutive, unselected stroke admissions, providing good generalisability of our results to the wider population.

However, I acknowledge some limitations of our study. Most notably, around 20% of our sample did not have pre-stroke mRS scores. Further analyses revealed that there were no significant differences of characteristics in the missing-data group compared with the data-intact group with the exception of stroke-type. Missing mRS data were more common for the severe stroke types (TACS & PACS). For a clinical registry, this pattern of missing data is not surprising. The more severe strokes will be less able to engage in assessments of pre-stroke status. Although these missing data create a potential bias, the effect is likely to have reduced the associations between pre-stroke mRS and outcome, rather than exaggerated it. Furthermore, the internal relationship and effect sizes observed between pre-stroke mRS and other measures are not affected by missing data. I acknowledge that we have no detail on how pre-stroke mRS was applied at each site. In the absence of explicit guidance on scoring, there is the potential for inter-rater variability in pre-stroke mRS. However, potential for variation in scoring is an issue for mRS per se, (108) and our data will reflect the way in which pre-stroke mRS is currently used in clinical practice, giving our results 'real world' validity. Finally, our validation analysis is limited by an imperfect reference standard: constructs such as place of residence are a blunt indicator of functional status.

In our analysis of the pre-stroke state we were limited to those assessments that had been routinely collected in our dataset. We did not have comprehensive data on potentially important covariates such as NIHSS. There is no single screening tool that will perfectly describe global functional ability. Assessments scales such as the Informant Questionnaire for Cognitive Decline in the Elderly (76) and Barthel Index (208) have been used to capture pre-stroke cognitive and physical ability and it is unfortunate that these data were not routinely collected during the period of our study. Nonetheless, in the absence of a clear 'gold standard' of pre-stroke function, the correlations with all of our measures in combination provides us with confidence in our validation method.

Based on our findings I offer guidance for clinicians and researchers. As a standard mRS is only a moderately valid measure of pre-stroke function, I would caution against using this as the sole criterion for assessing suitability for research or for interventions. To try and improve consistency I would recommend following published guidance and best practice in assessment.(106) A more comprehensive assessment of pre-stroke function could include measures of ability to perform activities of daily living and cognitive function. These assessments need not necessarily add substantial time to assessment, for example a short form Barthel Index for use in stroke has been described.(208) I would encourage greater use of pre-stroke measures in clinical practice, our data on the prognostic utility of mRS reminds us of the importance of considering the pre-stroke state.

There are plausible methods to improve the validity of pre-stroke assessment, and future research could focus on these areas. If we continue to use mRS, there may be scope to further operationalise the assessment. Structured questionnaire approaches to mRS have been described (209) and a similar approach to pre-stroke mRS could have utility. As mRS was never designed as a tool to measure pre-stroke function, perhaps we should move to a more relevant measure. There is increasing interest in tools to describe frailty (118) and these may have particular utility in an older adult stroke cohort.

6.5 Conclusions

In conclusion, we have assessed the prognostic predictability of the pre-stroke mRS and its validity as a measure of pre-stroke function. In combination, these results highlight that the pre-stroke mRS can reliably be employed as a tool to assist clinicians in service delivery and planning. We found that the pre-stroke mRS is a moderately valid measure of pre-stroke disability and a robust predictor of post-stroke prognosis. In combination, these results highlight that the pre-stroke mRS can reliably be employed as a tool to assist clinicians in service delivery and planning. The robust nature of the relationship between pre-stroke mRS and a number of different outcomes suggests that the pre-stroke mRS not only gives an insight into likely mortality or duration in hospital, but may also predict the probability that patients will need to be taken into care post-stroke,

as well as potential post-stroke complications experienced during the recovery period. Importantly, the prognostic accuracy of the pre-stroke mRS does not appear to be related to any variation in the process of care. Thus, prognostic models of stroke which incorporate pre-stroke mRS are likely to have potential for future clinical implication.

Chapter 7. The prevalence of frailty amongst acute stroke patients, and evaluation of method of assessment.

7.1 Introduction

Stroke and frailty are prevalent conditions in the elderly and are associated with mortality, long-term hospitalisation, and disability. (11, 210-214) Frailty assessment is increasingly being incorporated into routine practice in the acute care setting. (215) As I highlighted in chapter 2, section 2.4, frailty may have a relevance to our understanding of cognition in stroke. However, the prevalence of frailty and methods for frailty assessment are largely unstudied in the acute stroke population. Moreover, as discussed in chapter 6, pre-stroke function is often utilised in stroke trials and for assessing suitability for aggressive treatments in stroke; yet, my findings suggest that the pre-stroke mRS is a limited method for assessing pre-stroke function, and assessment of frailty may be a more relevant measure for these purposes. Hence, establishing frailty prevalence and validation of assessment is of importance in stroke.

There are variable methods of frailty assessment, depending upon the definition applied. A Frailty Index can be calculated as a measure of cumulative deficits. (119) Alternatively, the frailty phenotype can be detected via self-report questionnaire. (120)

I aimed to describe the prevalence of pre-stroke frailty in a 'real world' acute stroke setting and validate a commonly used method for determining frailty status. My primary focus was frailty assessment using the Rockwood Frailty Index approach. I then assessed concurrent, predictive and convergent validity of the Frailty Index. To allow comparison, I also assessed frailty as measured by a phenotypic (Fried) approach and using the mRS as a pre-stroke disability assessment.

7.2 Method

I conducted a secondary analysis of prospectively collected, cross-sectional, anonymised patient level data contained within the Glasgow Royal Infirmary patient database. Full NHS research ethics approval was granted for this project (ws/16/0001). The design, conduct and reporting of this study was informed by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) (216) and STROND (Standards of Reporting of Neurological Disorders) guidance. (217)

7.2.1 Setting and population

I recruited patients consecutively admitted to the acute stroke unit at a single urban teaching hospital. The unit is part of a nationally funded healthcare service and admits all stroke and transient ischaemic attack (TIA) patients and operates no exclusions around age, disability or comorbidity.

Patient recruitment occurred from May 2016 to Aug 2018. All patients with stroke or TIA were included. Ethical approvals allowed for inclusion of patients who were unable to consent to assessment.

7.2.2 Clinical and demographic information

Clinical and demographic data were collected for each patient at point of assessment by trained researchers. Assessments occurred on day of admission up to 7 days after admission. Data collected were a mix of prospective assessment and retrospective chart review. Pre-stroke functioning was established using mRS;(218) where a cut-off of ≥ 2 was used to define disability. In addition, stroke severity was determined by National Institutes of Health Stroke Scale (NIHSS);(130) delirium was assessed via the '4A Test' screening tool 4AT (www.the4AT.com); a cut-off of ≥ 4 was used to define a positive screen for delirium. Pre-stroke cognition was determined via medical history (prior diagnosis of mild cognitive impairment or dementia) and, where possible, informant assessment via the informant section of the Geriatric Practitioner

assessment of Cognition (GPCOG)(219) utilising a cut-off score of ≥ 3 (out of 6) as indicative of previous cognitive impairment. Age, medication count, and pre-stroke care-home residence were established via medical notes.

7.2.3 Pre-stroke frailty assessment

I utilised two methods for assessment of pre-stroke frailty; one conformed to the Rockwood accumulated deficits concept, the other to the Fried ‘frailty phenotype’ model. Based on the former, a 33-item Frailty Index was created according to recommended guidelines.(122) (see Appendix 20) Patient medical records were used to identify medical conditions present before the stroke. Frailty Index scores were then generated for all patients by two researchers (MT and GC). I created a list of 33 frailty indicator conditions, symptoms or problems. The Frailty Index was created by dividing the number of pre-specified conditions on our list that were present before the stroke by the total number of conditions defined in the index list (i.e. 33). Thus, possible scores ranged from 0.0-1.0, with scores closer to 1.0 suggesting greater frailty. If multiple instances of a medical condition were present (e.g. multiple falls, multiple diagnoses of cancer), these would be scored once and once only (i.e. a patient with a medical history consisting of 1 previous fracture and 2 previous diagnoses of cancer would generate a score of 2/33, not 3/33). Patients were categorised as ‘robust’, ‘pre-frail’ and ‘frail’ using recommended cut-points of <0.08 ; $0.08-0.24$ and >0.24 , respectively.(220)

An assessment of Fried phenotype frailty was added to the prospective dataset after first wave data collection was complete. I used the self-report ‘Frail non-Disabled’ questionnaire.(221) (see Appendix 21) This frailty assessment method was introduced to complement (and did not replace) the Frailty Index assessment method. Patients were categorised as frail if they and/or a proxy reported any one of the following: unintentional loss of more than 4kg of weight over the previous year; self-reported exhaustion for more than two days in the week before admission; less than 4 hours of physical activity over a 2-week period before admission. Patients who could not fully complete the self-report Frail non-Disabled questionnaire for any reason (e.g. unconscious, too confused, severely aphasic) were deemed non-testable.

7.2.4 Analyses

For analysis of prevalence of pre-stroke frailty, I performed a sample size calculation based on the formula:

$$N = \frac{(z^2)P(1 - P)}{d^2}$$

Where N represents the sample size; z is the z-statistic for the level of confidence (1.96); P is the expected prevalence (0.15); and d is the allowable error (0.05).

I required a minimum of 196 participants to give us an estimate of prevalence with 95% confidence.

I described prevalence of ‘frailty’, ‘pre-frailty’ and ‘robust’ status based upon observed percentages within the population; confidence intervals were generated for each prevalence estimate via z-tests. As Frail non-Disabled questionnaire data were only available for a proportion of patients, I conducted a post-hoc logistic regression analysis with Frail non-Disabled (testable/untestable) as the dependent variable and stroke severity (NIHSS score) as the independent variable to examine cause of missing frailty phenotype data.

To evaluate the Frailty Index as a measure of frailty in stroke I conducted a series of validity assessments. I assessed concurrent validity by exploring associations between Frailty Index and a series of factors plausibly related to frailty: age, sex, (222) number of medications, pre-stroke cognitive impairment and care home residence. I used Spearman’s correlation for continuous variables and Chi-square for dichotomous variables.

I assessed predictive validity of the Frailty Index as a measure of pre-stroke frailty based on associations with a common complication of stroke that frail patients are typically vulnerable to—post-stroke delirium. I used a logistic regression analysis with incident delirium as the dependent variable and score

on Frailty Index as the independent variable. As frail patients are generally vulnerable to acute stressors, I also examined if pre-stroke frailty was associated with stroke severity (NIHSS) using linear regression analysis with score on NIHSS as the dependent variable and Frailty Index as the independent variable. I then used multiple regression analyses, controlling for age, sex, and number of medications to further explore the associations between scores on the Frailty Index and delirium and stroke-severity. All variables were forced into the regression model.

I assessed convergent validity describing Chi-square correlation between Frailty Index (dichotomised: frail/non-frail), phenotypic frailty (dichotomised: frail/robust) and pre-stroke modified Rankin Scale (dichotomised: disabled/non-disabled). I also explored agreement between the measures using Kappa statistics; and overlap in frailty assessment results were compared for the differing frailty measures via 2x2 tables and Venn diagram.

I used SPSS statistics for Windows, version 24.0, Armonk, NY: IBM Corp, for all analyses.

7.3 Results

Five-hundred-forty-six patients were included. Population descriptive statistics can be seen in Table 7-1.

Table 7-1. Population demographics

	(Total included=546)
Age (Years) (Mean; S.D.)	69 (14)
Sex (Male) (Number; %)	290/540 (54%)
National Institutes for Health Stroke Scale (Median; IQR)	3 (1-5)
Pre-stroke modified Rankin Scale ≥ 2 (Number; %)	216/524 (41%)
Pre-stroke cognitive impairment (Number; %)	49/277 (18%)
Pre-stroke medication count (Median; IQR)	7 (4-10)
Pre-stroke care-home resident (Number; %)	21/546 (3.8%)
Post-stroke delirium* (Number; %)	138/523 (26%)

*Diagnosed based on stroke physician impression guided by the '4 A's test' using cut-point of ≥ 4 . S.D.= Standard deviation; IQR=Interquartile range.

7.3.1 Frailty prevalence

Frailty Index data were available for 545/546 (99.8%) patients of whom 151/545 (28%; 95% Confidence Intervals [CI]:24%-31%) were frail according to Frailty Index. A further 276/545 (51%) were pre-frail and 118/545 (22%; 95%CI:46%-55%) were robust. Median Frailty Index score was 0.18 (Inter Quartile Range [IQR]=0.09-0.26).

Phenotypic frailty data were available for 258/347 patients; 89/347 (26%) patients' full data were missing due to inability to complete the Frail non-Disabled questionnaire. Of patients with data available, 72/258 (28%; 95%CI=23%-34%) were frail. My post-hoc logistic regression analysis indicated that more severe strokes were associated with non-completion of the Frail non-Disabled questionnaire (Odds Ratio [OR]=1.21, 95%CI=1.13-1.29; $p<0.01$).

7.3.2 Concurrent validity

Frailty Index scores were significantly associated with all pre-specified pre-stroke variables. Specifically, older patients, women, patients on higher numbers of medication, patients with pre-stroke cognitive impairment, and patients in a care home had significantly higher Frailty Index scores. Strength of correlations are described in Table 7-2.

7.3.3 Predictive validity

Frailty Index was significantly associated with both the NIHSS (Unstandardised Beta=0.085, 95%CI=0.046-0.125; $p<0.01$) and incident delirium (OR=1.06, 95%CI=1.04-1.08; $p<0.01$) on univariate analysis. Specifically, as Frailty Index scores increased so too did NIHSS scores and odds of delirium. However, after controlling for age, sex and medication count, the associations were no longer significant. (Table 7-3)

Table 7-2. Correlations between pre-stroke variables and Frailty index

Variable	Frailty Index (Mean score)	Correlation (X ² /Rho; p-value)
Sex (Female)	0.19	9.19; <.0.01*
Sex (Male)	0.16	
Pre-stroke care-home resident (Yes)	0.31	30.92; <0.01*
Pre-stroke care-home resident (No)	0.17	
Pre-stroke cognitive impairment (Yes)	0.25	15.92; <0.01*
Pre-stroke cognitive impairment (No)	0.18	
Age (Years)	NA	0.54; <0.01#
Medication count (Number)	NA	0.58; <0.01#

*Analysed via Chi-square test (frailty dichotomised at >0.24); #Analysed via Spearman's Rho test (Frailty as continuous scale).

Table 7-3. Regression analysis of the association of the Frailty Index with stroke severity (NIHSS) and odds of post-stroke delirium onset

Regression variable	NIHSS (Beta)*	(p)	Delirium (OR; 95%CI)%	(p)
Frailty Index (Score)	0.09	0.21	1.03 (1.00- 1.05)	0.05
Age (Years)	0.21	<0.01	1.06 (1.04- 1.08)	<0.01
Sex (Female)	-0.01	0.92	0.86 (0.54- 1.37)	0.53
Medication count (Number)	0.01	0.93	1.01 (0.94- 1.71)	0.85

*Linear regression; %Logistic regression. All variables were forced into the model. NIHSS = National Institutes of Health Stroke Scale. Frailty entered as continuous variable.

7.3.4 Convergent validity

For the 258 patients with Frail non-Disabled questionnaire data available, the Frailty Index demonstrated a moderate positive correlation with the Frail non-Disabled questionnaire ($X^2=15.76$; Cramer's $V=0.25$). Similarly, for the 524 patients with pre-stroke modified Rankin scale data available, the Frailty Index demonstrated a moderate correlation with the pre-stroke modified Rankin scale ($X^2=116.55$; Cramer's $V=0.47$).

There was only slight agreement between Frailty Index and phenotypic frailty ($\kappa=-0.06$) with just 16/81 (20%) frail patients categorized as frail on both frailty measures. (Table 7-4) For Frailty Index and pre-stroke modified Rankin Scale, agreement was moderate ($\kappa=0.45$) with 110/216 (51%) patients classified as disabled according to pre-stroke modified Rankin Scale also classified as frail according to the Frailty Index. There was only slight agreement between phenotypical frailty and modified Rankin Scale ($\kappa=-0.02$) with 28/68 (41%) patients classified as phenotypically frail being classified as disabled according to the mRS. (Figure 7-1)

Figure 7-1. Frailty and disability overlap based on method of assessment

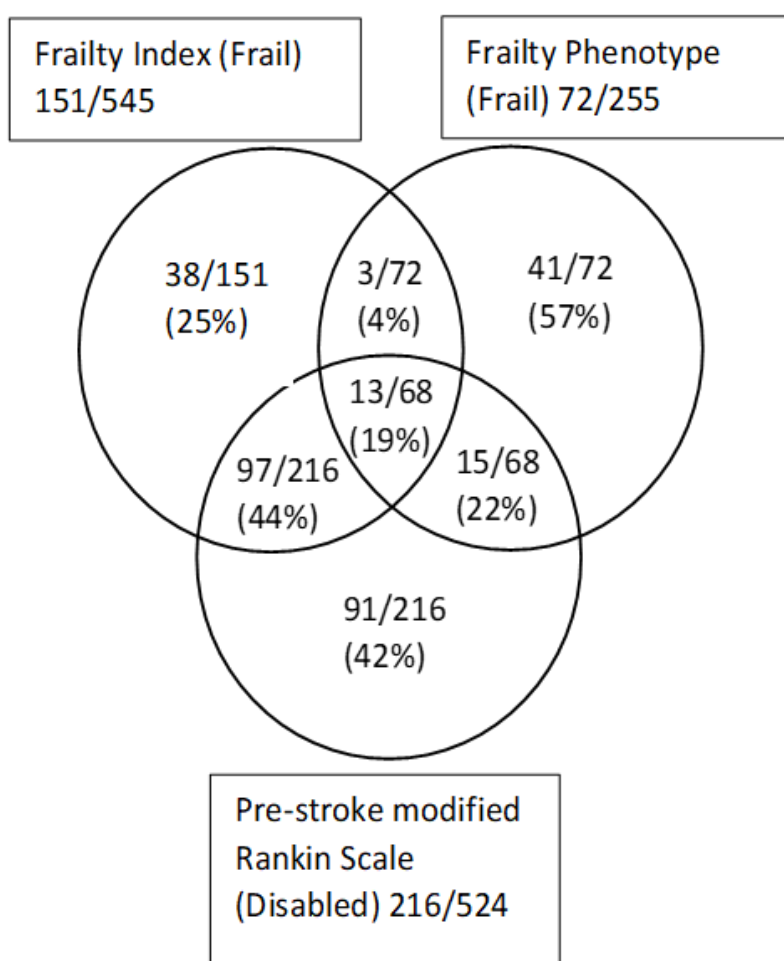


Table 7-4: Agreement between frailty/disability measures

	Frailty Index	Frail non-Disabled questionnaire	Modified Rankin Scale
Frailty Index		86	281
Frail non-Disabled questionnaire	16		78
modified Rankin Scale	110	28	

White cells correspond to frailty positive comparisons; grey cells to frailty negative comparisons.

7.4 Discussion

7.4.1 Prevalence

I sought to investigate the prevalence of frailty in stroke. I found that almost 80% of patients admitted to an acute stroke unit were either frail or pre-frail according to Frailty Index criteria. Both the Frailty Index and frailty phenotype approach gave respective prevalence rates of 28%. These rates contrast with the 14% rate reported within a non-stroke hospital population and the 11% prevalence reported in community settings.(114, 223) My results suggest that frailty presents a particularly significant burden in stroke, beyond what is typically observed in undifferentiated older adult populations. The pre-frail categorisation is contentious, but that more than half of our sample were considered pre-frail before the stroke is particularly relevant. These patients may be at risk of becoming frail following stroke, with the stroke event pushing many across a threshold from 'pre-frail' to 'frail' status.

7.4.2 Frailty assessment

There are different ways to measure frailty. I chose to primarily evaluate the Frailty Index approach as this has been well validated in other acute settings and is being adopted in acute care settings; I also anticipated that it would be available for the majority of stroke admissions. My intention was not to create a novel tool, rather I operationalised a Frailty Index using the same process that was used to develop the electronic Frailty Index that is being introduced in NHS England.(121)

Concurrent validity analyses was reassuring, confirming Frailty Index associations with variables previously demonstrated to be associated with frailty (age, sex, medication count, pre-stroke cognitive impairment and care-home residence).(220, 223-225) The core concept in frailty is vulnerability to an acute stressor, with adverse outcomes when the person is exposed to acute illness or other insult. In this regard, my assessment of the association of frailty and incident delirium offers the most compelling validation, as delirium is considered

an exemplar manifestation of the frailty state, albeit this association did not hold after controlling for additional variables.

Comparative analyses suggest that method chosen for assessing frailty in stroke is important. There were only modest correlations between the Frailty Index, the phenotype measure and pre-stroke modified Rankin Scale. Similar correlations were found by Rockwood's group in an earlier paper.(220) Although prevalence rates suggested by our two frailty measures were similar, there was little agreement regarding which patients were classified as frail: only 20% of frail patients were categorised as such by both frailty measures and kappa based measures of agreement were little better than chance. These findings may be partly explained by non-completion bias for the phenotype measure, although previous studies have also highlighted issues with frailty identification based upon definition and assessment methods used. As few as 9.4% of frail patients were categorised as such by both a frailty phenotype and Frailty Index measure in one study;(226) while others reported that 30% of patients categorised as frail by an Frailty Index were categorised as 'robust' according to a Fried phenotype measure.(224) This lack of agreement likely reflects the differences in the respective concepts of frailty that are applied by our two measures. My analyses were not designed to suggest a favoured approach to frailty assessment. An important assessment in this regard would be to compare post-stroke outcomes according to frailty defined using differing models and this could be the basis for future research around stroke and frailty.

7.4.3 Strengths and limitations

This is a highly inclusive study with sequential recruitment involving patient groups (e.g. aphasic, acutely unwell, physically disabled, cognitively impaired) that are typically excluded from stroke studies. I have also incorporated frailty measures assessing the two predominant frailty concepts.

However, there are some important limitations to this study. First of all, while inclusive, the population was restricted to a single urban teaching hospital that admits a largely socioeconomically deprived and Caucasian population. As such, the observed frailty prevalence rates may not be generalisable to settings with a

very different case-mix.(227) The measure of the frailty phenotype may be more indicative of frailty symptoms rather than full phenotypical frailty per se. Moreover, this measure was introduced during study recruitment and could have been biased by missing data. Finally, comparisons between ‘phenotypic’ and ‘cumulative deficits’ frailty models should recognise that the two measures were never designed to be equivalent. The Frail non-Disabled scale is intended to be used as a screening tool and its properties will differ from a Frailty Index, which is said to be diagnostic.

7.4.4 Clinical and research implications

The timely, accurate and acceptable identification of frailty in practice is a current clinical priority.(228-230) Advances have been made in frailty assessment in community, care-home and older adult secondary care settings, but it is equally important to determine the most suitable methods of assessing frailty in stroke. My results are not definitive and further epidemiological and validation work around frailty assessment and stroke is required. While it would be premature to make recommendations around practice or policy based on our data, I can offer cautious suggestions. The high prevalence of frailty and pre-frailty reminds us that vulnerable, older adults are core business in stroke-care. There is a danger that this may be forgotten in the move towards increasingly aggressive interventional strategies for acute stroke. The relationship of frailty with the complication of incident delirium may suggest that a brief frailty assessment could become part of the initial ‘work-up’ in stroke. This would mirror changes in practice in other healthcare settings where front-door frailty screening is being introduced.

My results have implications for research. Pre-stroke modified Rankin Scale is often used as exclusion criterion or case-mix adjustor in stroke trials. The modified Rankin Scale was never designed for this purpose and, as suggested in chapter 6, it may not be the best measure as it may both under and over-estimate function. Using a simple measure of frailty as a baseline measure in trials could improve efficiency and our data suggest that assessing a Frailty Index is relatively simple in an inpatient stroke population.

7.4.5 Future directions

Future studies of frailty in stroke should offer longitudinal follow-up to determine the longer-term prognostic validity of frailty measures. Frailty has previously been associated with long-term prognosis in older adult populations.(231) It is highly likely that this will also be the case in the stroke population; hence, this is an important area for future research. Finally, this work suggests that different tests of frailty may be assessing differing constructs. We now need more comparative studies of the different frailty measures (and concepts) when used in the stroke population.

7.5 Conclusions

The prevalence of frailty in acute stroke is substantial; the condition appears to exist, before the stroke occurs, in around one in every four patients, or around three out of every four patients if pre-frailty is included. Identification of frailty may be influenced by assessment method employed. My results suggest that the Frailty Index approach is valid for use in stroke and can be employed for assessment of almost all stroke patients; albeit, it has limited agreement with other measures of frailty. More research is needed to describe the optimal method of assessing frailty and the prognostic and treatment implications when a frailty diagnosis is made in stroke.

Chapter 8. Investigating the risk association between pre-stroke frailty and acute post-stroke cognition.

8.1 Introduction

In order to understand the aetiology of post-stroke cognitive impairment it is important to identify pertinent risk factors.

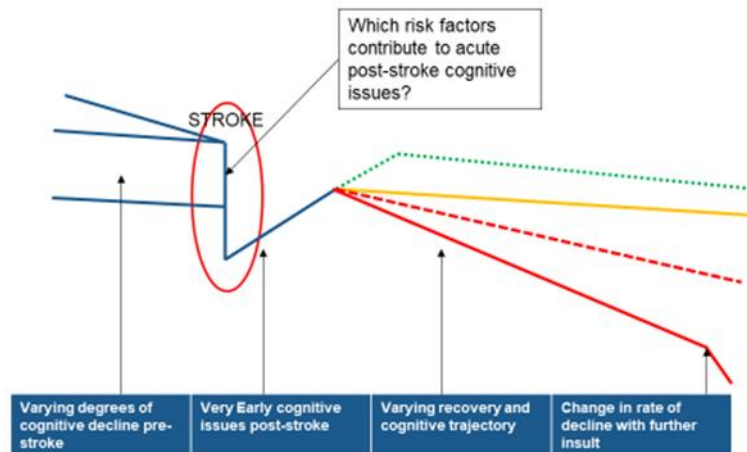
Frailty has been associated with development of cognitive impairment (232), delirium (113) and vascular dementia (233) in non-stroke populations. As discussed in chapter 2, section 2.4 there are reasons to expect that frail patients may experience greater cognitive impairment following stroke than non-frail patients.

Specifically, the Rockwood ‘accumulated deficits’ concept, proposes that frailty arises from the increasing burden of age-related medical conditions that accrue over the life-time. (111) This accumulation may lead to a state of physiological exhaustion and impaired repair mechanisms, thus limiting the body and brain’s ability to respond to, and minimise the damage of, further stressors.(116) As stroke is a cognitive stressor, the state of vulnerability induced by frailty may heighten the cognitive consequences experienced by patients in the aftermath of the event.

Having established in chapter 7 that pre-stroke frailty is prevalent and can be identified in most patients using the Frailty Index approach, I therefore sought to assess the relationship between pre-stroke frailty and post-stroke cognition in the acute period following stroke (see Figure 8-1). It is possible that any association between frailty and post-stroke cognition may be accounted for by differences in confounders such as age, pre-stroke cognitive impairment, and onset of delirium. I aimed to investigate if an association between frailty and post-stroke cognition was independent of these and other variables that are typically associated with post-stroke cognitive impairment.

I hypothesised that pre-stroke frailty would be significantly associated with lower post-stroke cognition and that this association would be independent of other well-established moderators of post-stroke cognitive impairment.

Figure 8-1. The aetiology of acute cognitive impairment following stroke is yet to be fully determined.



8.2 Method

I conducted a cross-sectional study, using the Glasgow Stroke Research Database (GSRD). The GSRD allows collection of anonymised patient level data and has full research ethics approval (ws/16/0001).

I followed guidelines proposed by Riley et al., (2009) (234) regarding prognostic factor research related to the design, conduct and analysis of this study. I followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidance for reporting. (235) The protocol for this study was registered at Research Registry (UIN: researchregistry2712).

8.2.1 Setting and Population

I utilised the population described in chapter 7 section 7.2.1 However, at the time this study was conducted, recruitment was still ongoing; hence only patients admitted between May 2016 and December 2017 were included. Moreover, this study had further inclusion/exclusion criteria to that described in chapter 7 section 7.2. Specifically, to be included in analysis patients required a stroke diagnosis confirmed by a stroke clinician and a cognitive assessment

within seven days post-stroke. I did not exclude any patients based upon age or presence of aphasia, dysarthria, previous cognitive impairment or physical or sensory disability. However, patients were excluded from analyses if they had a TIA or non-stroke diagnosis or were unable to fully complete the cognitive assessment for any reason.

8.2.2 Clinical and demographic information

As described in chapter 7, clinical and demographic information was collated for each patient by trained researchers via patient self-report and medical records. Stroke diagnosis and stroke-type (using Oxford Community Stroke Project (OCSP)) (48) was confirmed by a stroke consultant. Stroke severity was derived via National Institutes for Health Stroke Scale (NIHSS); where the NIHSS had not been completed, scores were generated via retrospective review of medical charts (130). Although retrospective review of medical charts is not the optimal means of establishing an NIHSS score, it has been established to be a valid, reliable means of assessment. (131, 236)

Delirium was assessed via the '4A Test' screening tool 4AT (www.the4AT.com); a cut-off of ≥ 4 was used to define a positive screen for delirium. Pre-stroke cognition was determined via medical history (prior diagnosis of mild cognitive impairment or dementia) and, where possible, informant assessment via the informant section of the Geriatric Practitioner assessment of Cognition (GPCOG) (219) utilising a cut-off score of ≥ 3 (out of 6) as indicative of previous cognitive impairment.

8.2.3 Cognitive assessment

All patients admitted to the acute stroke unit also underwent a short cognitive assessment utilising a mini-Montreal Cognitive Assessment (MOCA) to generate a total score out of 12 points. (127) Higher scores indicate better cognition. The assessment covered the cognitive domains of episodic memory (5-word recall), visuospatial and executive functioning (clock draw), language (verbal fluency test) and orientation (date). (see Appendix 4)

8.2.4 Pre-stroke Frailty assessment

I used the Frailty Index, as described in chapter 7, section 7.2.3, for pre-stroke frailty assessment.

8.2.5 Statistical analysis

I used bespoke software (G-Power, version 3.1; (237)) to inform a sample size calculation for multiple linear regression. Based on inclusion of 8 important independent variables, a clinically useful, moderate, effect size of $F^2 = 0.10$, power of 0.80 and a statistical significance level of 0.05, I required a sample size of 159 participants for analysis.

I performed a univariate linear regression analysis, with 'score on cognitive testing' as the dependent variable and pre-stroke Frailty Index score (continuous) as the independent variable. Linear multiple regression analysis was then conducted, adjusting for important covariates that were deemed likely to vary by frailty status and/or impact upon post-stroke cognition. (37, 232, 238, 239) Included covariates were age, sex, stroke severity, stroke-type (lacunar/non-lacunar), previous stroke/TIA, delirium, and previous cognitive impairment. Stroke-type was categorised as a nominal variable with 2 levels (Lacunar/non-lacunar) on the basis that lacunar strokes and cortical strokes may differentially impact cognition.(49) Each covariate was forced into the model regardless of significance in univariate analysis.

CLINE (constant variance, linearity, independence of observations, normality of residuals & error-free values) assumptions were checked for each model. Multi-collinearity between continuous variables was also assessed.

All models were created using SPSS statistics for Windows, version 24.0, Armonk, NY: IBM Corp.

8.3 Results

8.3.1 Patient characteristics

Of 262 confirmed stroke (this figure does not include confirmed TIA's admitted) patients admitted during recruitment waves between May 2016 and Dec 2017, full data were available for 154 patients (59%). Ninety-four (36%) patients were excluded due to being untestable on cognitive assessment, and 14 (5%) were excluded due to not completing a cognitive assessment within 7 days following admission. Mean Frailty Index score for the population was 18 (S.D.= 11; range= 0-53); mean age of included participants was 68 years (S.D.= 13; range=32-97); median score on cognitive assessment was 8 (IQR=4; range= 0-12); median stroke severity was 2 (IQR=3; range=0-21); 92/154 (60%) were male; frailty prevalence based upon Frailty Index dichotomisation at a Frailty Index score of >24 was 51/154 (33%); 54/154 (35%) of stroke types were partial anterior circulation strokes (PACS); 36/154 (23%) had a previous stroke/TIA; 13/154 (8%) were cognitively impaired before the stroke (informant assessment data was available for 72/154; 47%); 13/154 (8%) screened positive for post-stroke delirium. Full demographic and clinical data for patients can be seen in Table 8-1.

Table 8-1. Descriptive statistics

	Number	Range	Mean/median (S.D.; IQR)
Frailty Index (Score)	154	0-53	18 (11)
Age (Years)	154	32-97	68 (13)
Mini-MOCA (Score)	154	0-12	8 (IQR=4; 25 th =6 75 th =10)
NIHSS (Score)	154	0-21	2 (IQR=3; 25 th = 1 75 th =4)
	Number	%	
Sex (Male)	93/154	60	
Frailty Index dichotomised (Frail >0.24)	51/154	33	
Stroke Type			
TACS	8/154	5	
PACS	54/154	35	
LACS	50/154	32	
POCS	36/154	23	
Unclassified	7/154	5	
Pre-stroke cognitive impairment (Impaired)*	13/154	8	
Delirium (Screened Positive)	13/154	8	
Previous stroke/transient ischaemic attack (Yes)	36/154	23	

Mini-MOCA= Mini Montreal Cognitive Assessment; NIHSS= National Institute of Health Stroke Scale; TACS= Total Anterior Circulation Stroke; PACS= Partial Anterior Circulation Stroke; LACS= Lacunar Stroke; POCS= Posterior Circulation Stroke; *Prior diagnosis of Mild Cognitive Impairment or Dementia or $\geq 3/6$ on General Practitioner Cognitive Assessment- informant section questionnaire.

8.3.2 Associations with cognitive status after stroke

Results of the univariate and multiple linear regression analyses are presented in Tables 8-2 & 8-3.

Pre-stroke frailty was significantly associated with post-stroke cognition (Standardised-Beta= -0.40, $p<0.001$) based on univariate linear regression. As Frailty Index scores increased, cognitive scores declined. Age, sex, NIHSS, delirium, pre-stroke cognition and stroke-type were all associated with post-stroke cognitive score based on univariate analysis (all $p<0.05$). Previous stroke/TIA was not ($p=0.65$).

After adjusting for covariates, the association between frailty and post-stroke cognition remained significant (Unstandardized Beta= -0.05; Standardised beta=-0.21; $p=0.005$). Additional independent variables associated with post-stroke cognition were age (Unstandardized Beta= -0.05; Standardised beta =0.24; $p=0.002$), pre-stroke cognitive disorder (Unstandardized Beta= -2.28; Standardised beta=-0.22; $p=0.001$), delirium (Unstandardized-Beta= -2.81; Standardised-Beta= -0.27; $p<0.001$), and stroke severity (NIHSS) (Unstandardized Beta= -0.19; Standardised beta =-0.22; $p=0.001$). Stroke-type ($p=0.30$), previous stroke/TIA ($p=0.77$) and Sex ($p=0.57$) were not significantly associated with post-stroke cognition. The combined model explained 43.5% of the variance in cognitive scores (adjusted R-square=0.435) at $p<0.001$.

Tests of assumptions for the model revealed collinearity between Frailty Index scores and age. However, multicollinearity was not a problem in the model according to variance inflation factor (VIF) scores (all <2) (see Table 8-4). All other assumptions were satisfied (see Figure 8-2).

Table 8-2. Univariate analysis results of selected variables association with cognition

Variable	Unstandardized Beta	Standardised Beta	Significance (p)
Frailty Index (Score)	-0.10	-0.40	<0.001
Age (Years)	-0.10	-0.47	<0.001
Sex (Female)	-1.05	-0.18	0.026
Stroke severity (NIHSS)	-0.32	-0.37	<0.001
Stroke-type (Lacunar)	1.08	0.18	0.030
Pre-stroke cognitive impairment (Impaired)	-3.45	0.33	<0.001
Delirium (Yes)	-3.95	0.38	<0.001
Previous stroke/transient ischaemic attack (Yes)	-0.25	-0.04	0.654

Dependent variable=Montreal Cognitive Assessment score. Stroke-type was categorised as a nominal variable with 2 levels (Lacunar/non-lacunar). Frailty Index, Age, and Stroke severity were entered as continuous variables. NIHSS= National Institute for Health Stroke Scale.

Table 8-3. Multiple Linear regression output of selected variables' associations with post-stroke cognition

	Adjusted R-square		Significance (p)
	0.44		<0.001
Variable	Unstandardized Beta	Standardised Beta	Significance (p)
Frailty Index (Score)	-0.05	-0.21	0.005
Age (Years)	-0.05	-0.24	0.002
Sex (Female)	-0.22	0.04	0.567
Stroke severity (NIHSS)	-0.20	-0.23	<0.001
Stroke-type (Lacunar)	0.41	0.07	0.295
Pre-stroke cognitive impairment (Impaired)	-2.28	-0.22	0.001
Delirium (Yes)	-2.81	-0.27	<0.001
Previous stroke/transient ischaemic attack (Yes)	-0.12	-0.02	0.774

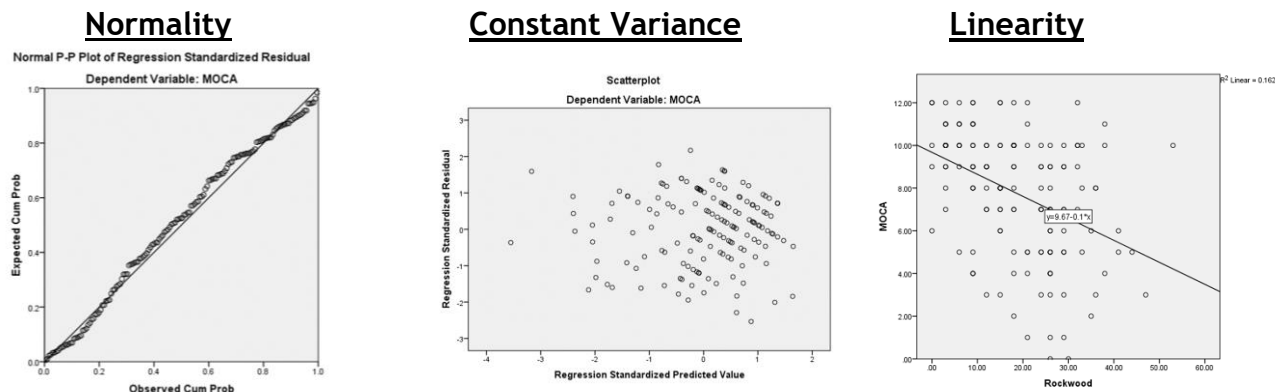
Dependent variable=Montreal Cognitive Assessment score. All variables were forced into the model. Stroke-type was categorised as a nominal variable with 2 levels (Lacunar/non-lacunar). Frailty Index, Age, and Stroke severity (NIHSS) were entered as continuous variables. NIHSS= National Institute for Health Stroke Scale.

Table 8-4. Results of test for multicollinearity in multiple regression model

Variable	Variance Inflation Factor (VIF)
Previous stroke	1.050
Frailty Index	1.434
Stroke Type	1.083
Pre-stroke cognitive impairment	1.076
Delirium	1.118
Age	1.561
Sex	1.188
NIHSS	1.121

*NIHSS= National Institutes of Health Stroke Scale

Figure 8-2. Tests of Assumptions



Footnote: PP plot and scatter plots indicate all assumptions were satisfied.

8.4 Discussion

8.4.1 Frailty-cognition association

I investigated the association between pre-stroke frailty and cognition in the acute period after stroke. Pre-stroke frailty was hypothesised to be independently associated with lower post-stroke cognition. My findings support this hypothesis.

Those patients who had higher levels of frailty before stroke demonstrated significantly lower cognitive scores than those with comparatively lower frailty. Moreover, the association was apparent even after adjusting for other well-established risk factors for post-stroke cognitive impairment, including those that often co-occur with frailty.

This frailty-cognition association is consistent with findings from non-stroke populations suggesting a potentially important clinical relationship between frailty and cognitive impairment. (232, 240)

It must be highlighted however, that the observed effect size for pre-stroke frailty was relatively small, and less than half of the overall variance in post-stroke cognition was explained by our model despite inclusion of eight predictors. This emphasises that a number of variables contribute in combination to the post-stroke cognitive state and no single variable is paramount to its outcome.

8.4.2 Mechanisms

There are several plausible mechanisms by which the observed association between pre-stroke frailty and poorer post-stroke cognition may have arisen. Frail patients may differ in pre-stroke brain reserve or levels of pre-stroke neuroinflammation—each of which could conceivably contribute to lower post-stroke cognitive performance. (241, 242)

Alternatively, the observed association may not be attributable to a few select mechanisms. Central to the accumulated deficits concept of frailty is that the 'system' of the body and brain is broken down due to an overabundance of problems. As the accumulation of deficits increase, physiological redundancy is reduced leading to exhaustion or impairment of the brain's repair mechanisms; thus, prohibiting ability to prevent or minimise further damage. The specific health deficits present matter little; more relevant is the overall number of deficits.(243) In this sense, when a plethora of general age-related health deficits combine, the brain may be left in a state of increased vulnerability to the cognitive consequences of a stroke.(116) This 'brain frailty' may in part explain frail patients' predisposition to delirium; however, it is noteworthy that patients with greater frailty in our study were still found to have lower post-stroke cognition even after controlling for presence of delirium post-stroke, suggesting that the association with lower post-stroke cognition itself cannot be attributed solely to delirium.

8.4.3 Strengths and limitations

I conducted an inclusive, exploratory study with an adequate sample size to investigate the association between frailty and post-stroke cognition, controlling for multiple relevant covariates. However, there are some important limitations worth mentioning.

First, there was no blinding to cognitive scores when generating pre-stroke frailty ratings for each patient, creating a potential risk of bias. In addition, it was not possible to control for some potentially important covariates that could influence the observed associations with post-stroke cognition, such as premorbid Intelligence Quotient (IQ). Moreover, our assessment of pre-stroke cognition was limited by missing data and as such the observed frailty-cognition association could be contributed to by the pre-stroke cognitive state. Finally, while the generalisability of included patients is heightened by our very limited exclusion criteria, there were few severe strokes included in our analysis and patients unable to complete cognitive assessment may often have been the more

severely cognitively impaired. Greater inclusion of such patients may influence the associations and effect sizes that we report.

8.4.4 Clinical implications and future directions

My findings emphasise that not all variables that predict post-stroke cognition are classically ‘psychological’. It is therefore important that clinicians are aware of the potential influence of frailty on post-stroke cognition and should consider incorporating the measurement of frailty into typical clinical assessment.

At present, our understanding of the frailty relationship with post-stroke cognition is limited by the cross-sectional nature of our study. Frail patients typically show less improvement or stabilisation in cognition over time compared to non-frail patients in general older-adult populations. (244) In this regard, the initial cognitive status combined with the frailty status of the patient could matter to future cognitive trajectories following stroke. The long-term effects of frailty on post-stroke cognition should therefore be investigated.

It would also be beneficial to determine if other concepts of frailty, for example the frailty phenotype (110), are also associated with post-stroke cognition. While many patients defined as frail according to the accumulated deficits concept will also be frail in a form consistent with the phenotype, as we found in chapter 7, agreement between these concepts is far from perfect; hence there may be differences in post-stroke cognitive risk based on frailty definition adopted. However, I would also note that there is a high likelihood that many stroke patients will not be able to complete a frailty phenotype assessment and will therefore be a challenge to investigate this form of frailty in a generalisable way.

Finally, replications of my results are important in order to establish if frailty is indeed associated with post-stroke cognition, independent of already established risk factors. If these findings are supported, future studies should assess and control for frailty when investigating post-stroke cognition as failure to do so could confound results.

8.5 Conclusion

There is evidence that frailty is associated with lower post-stroke cognition, independent of factors that have previously been associated with post-stroke cognitive impairment. When assessing post-stroke cognition, clinicians and researchers should be aware of this potential relationship. Future studies should investigate the influence of frailty on longer term trajectories of post-stroke cognition.

Chapter 9. Summary, discussion and conclusion

Psychological issues in stroke are recognised for their importance to overall stroke outcomes, but understanding these issues is still very much an ongoing task. In this thesis, I focused upon the relevance of the pre-stroke state and conducted a series of studies designed to enhance our knowledge of four pre-stroke conditions. The studies described in this thesis used various research methods, but all were designed to improve our overall understanding of the psychological issues that stroke survivors often experience.

9.1 Pre-stroke cognition

In chapter 2, section 2.1, I discussed how the lack of validation and guidance regarding optimal selection and use of informant tools in a pre-stroke context is a problematic area in stroke. I looked to address this issue in chapter 3 as part of a prospective, clinical, cohort study. I assessed the validity of two prominent informant tools, the IQCODE-SF and AD8, and found evidence to suggest that they are indeed valid when used to assess pre-stroke cognition. Both tools were near identical in their overall performance for detecting pre-stroke cognitive impairment (demonstrating AUROC~0.8), which, given its shorter duration and simplicity of scoring, may suggest an advantage of using the AD8 over the IQCODE-SF for pre-stroke cognitive assessment.

I also assessed performance of the two tools at recommended cut-points and determined whether these matched the optimal cut-point as indicated in my dataset. At their recommended cut-points, the two tools demonstrated contrasting strengths. The AD8 was more sensitive (86.7%) to any cognitive impairment than the IQCODE (62.1%), but the IQCODE was more specific (87.7% vs 70.8%). It is debateable whether sensitivity or specificity should be prioritised in pre-stroke assessment; however, what is clear is that use of these tools at their recommended published cut-points could conceivably result in contrasting participant pools.

Comparison of recommended published cut-points against optimal cut-points according to ROC curves suggest that both tools may perform better by altering the cut-point, dependent upon the population studied. When assessing for any pre-stroke cognitive impairment the IQCODE may perform better at a lower cut-point, while the AD8 may perform better at a higher cut-point when the intention is to restrict assessment to identifying dementia patients only. Diverging from recommended published cut-points is however contentious and has been a source of heterogeneity between studies in the past, likely contributing to the heterogeneous results often observed in the stroke-cognition literature. I would therefore suggest that it would be unwise for researchers and clinicians to diverge from the recommended published cut-points on the basis of these findings.

My results indicate areas for future research. A future systematic review and meta-analysis of performance at varying cut-points could potentially establish the optimal use of both the IQCODE and AD8 when used to assess pre-stroke cognition; however, this would require more studies of the type I conducted in chapter 3 to be completed first. At the moment, the study presented in this thesis is the first to validate the two tools for assessment of the pre-stroke state against a clinical gold standard. In addition, the prevalence of ‘any’ pre-stroke cognitive impairment (i.e. dementia plus cognitive impairment no-dementia) remains unestablished and would be beneficial for understanding the natural history and aetiology of post-stroke cognitive impairment. There also remains room for a qualitative study to determine the issues behind poor feasibility/acceptability of the IQCODE as described in chapter 2, section 2.1.

9.2 Pre-stroke depression

In chapter 2, section 2.2, I outlined 3 areas that are fundamentally lacking basic information in the context of pre-stroke depression: prevalence, risk association with post-stroke depression, and assessment methods. In chapter 4 I attempted to better establish the prevalence of pre-stroke depression and its risk association with post-stroke depression. I conceived, designed and conducted a systematic review and meta-analyses of the prevalence rates of pre-stroke

depression and odds ratios for presence of post-stroke depression, that are typically reported in the stroke-depression literature.

The prevalence rates I observed suggest that the stroke population may be more prone to depression than the general older adult population (17% vs 12%); but prevalence is ultimately considerably lower than the rate observed in a post-stroke context (30% at any time point). Moreover, the prevalence rate along with the apparent risk association observed adds further insight into the aetiology of post-stroke depression. Specifically, my findings seem in line with the notion that depression after stroke is primarily driven by the psychological and functional consequences of the stroke itself, yet emphasises that the pre-stroke state is a relevant predictor none-the-less. In my opinion, that depression before the stroke increases odds of depression after the stroke may also suggest that post-stroke depression is not predominantly vascular or lesion-location specific in nature. That is not to say a vascular source to some cases of post-stroke depression can be ruled out, but it is arguable that we should not expect a significant association between pre and post-stroke depression, if depression after the stroke is exclusively driven by vascular damage. There are of course limitations to my risk association meta-analysis that must temper any conclusions that can be drawn in this regard, but further work in this area could be beneficial.

While my work has helped to enhance our understanding of depression in the pre-stroke context, there are areas for future research to explore. Information regarding the predominant means of assessment of pre-stroke depression is still lacking. I was able to report the methods utilised in the studies included in my review; however, it was not designed to establish every means of assessing pre-stroke depression employed. Of the studies included in the review, I found medical records to be the most commonly employed method for identification of pre-stroke depression. I also found evidence to suggest that this may be a suboptimal means of detecting pre-stroke depression based on the significantly lower prevalence rates reported when utilising this method as compared to clinical interviews. In chapter 5 I therefore explored the use of informant tools as an alternative approach for pre-stroke depression assessment. I found some preliminary evidence that an informant approach to pre-stroke depression

assessment may be a useful approach. One particular tool, the GDS-SF, may have the pattern of sensitivity and specificity to be of clinical use in detecting pre-stroke depression. The validity of the GDS-SF has been questioned in the past however and the limited sample size in this study warrants a need for further investigation. There were also questions over the feasibility/acceptability of the GDS_SF based upon a high ratio of 'unknown' responses from informants when evaluating their relative's mood. The feasibility/acceptability and other psychometric properties of pre-stroke informant depression scales therefore require further study. I would argue that, at present, adopting an informant approach to pre-stroke depression assessment may only be advisable when the patient themselves cannot report upon their own mood.

9.3 Pre-stroke disability

In chapter 2, section 2.3, I discussed how pre-stroke disability may be relevant to post-stroke psychological outcomes but also that its relevance stretches beyond this. Pre-stroke disability is frequently assessed both clinically and in research to determine suitability for aggressive treatments and stroke trials. However, it is most commonly assessed via the mRS which was not designed for pre-stroke use and had not been well validated for this purpose. In chapter 6 I looked at the validity of the pre-stroke mRS through secondary analysis of clinical data held in an existing database. The findings of that study suggest that the pre-stroke mRS has modest validity based on correlations with other markers of function. It also showed that it has use as a prognostic indicator based upon associations with a number of poor outcomes. Moreover, these associations could not be explained by a difference in post-stroke care-pathway. Overall, the results suggested that the pre-stroke mRS is a valid measure for pre-stroke disability assessment; however, it is not optimally suited for this purpose.

These findings demonstrate a need for further work in relation to pre-stroke functional assessment. I think that the pre-stroke mRS would benefit from standardised instructions for its use. This could help not only improve its validity, but also important additional psychometric properties such as inter-rater reliability and is an approach that already exists for post-stroke mRS

assessment.(245) The field may also benefit from exploring alternatives to the mRS as a means of assessing pre-stroke disability. A more comprehensive pre-stroke functioning assessment could be of particular use as there is limited availability of gold standard assessments with which to evaluate the diagnostic test accuracy of the pre-stroke mRS.

In addition, the prevalence and risk associations between pre-stroke functioning and post-stroke psychological outcomes remain relatively unstudied. Future work in this area would benefit our wider understanding of psychological issues in stroke and the relevant factors associated with this.

9.4 Pre-stroke frailty

Frailty is a largely unstudied condition in stroke. It differs from pre-stroke function in that it implies a state of heightened vulnerability but does not necessarily involve disability. Frailty has demonstrated associations with cognitive conditions within the older adult population and in chapter 2, section 2.4, I discussed the need to establish prevalence and assessment methods for pre-stroke frailty along with a potential risk association with post-stroke cognition. I conceived and conducted 2 studies in chapters 7 and 8 to address these gaps in the literature. In chapter 7 I utilised a patient database at the Glasgow Royal Infirmary and conducted a secondary analysis of collected clinical data in order to investigate the prevalence of pre-stroke frailty and validate a commonly used frailty measure: the Rockwood 'Frailty Index'.

My results indicate a substantial burden of frailty in acute stroke, possibly occurring in as many as ~80% of patients if the 'pre-frailty' state is considered. The Frailty Index measure also appears to be valid as a measure of frailty and can be completed in the vast majority of stroke patients, in contrast to self-report frailty phenotype measures.

In chapter 8 I explored a possible risk association between pre-stroke frailty and acute post-stroke cognition, utilising the same approach as in chapter 7. My results indicated that frailty, as defined by the Frailty Index, was associated with lower acute post-stroke cognition and that this association was independent

of other established risk factors known to effect post-stroke cognition. This study was limited by difficulties of cognitive assessment in stroke and limitations regarding how accurately some of the covariates could be measured. However, it demonstrates an as yet previously unidentified variable as potentially being relevant to the post-stroke cognitive state.

Further work around frailty in stroke, particularly in relation to frailty and longer-term cognitive outcomes and trajectories could be of particular benefit to our understanding of the natural history and aetiology of post-stroke cognitive impairment. What is more, the influence of phenotypical frailty on post-stroke cognitive outcomes remains to be established and would also be a useful avenue for further research in this field.

9.5 Conclusion

In conclusion, I have investigated the pre-stroke state in order to better understand psychological problems in stroke. I have identified and addressed a number of gaps in the literature, but many remain. It is important for future research to consider the pre-stroke state as it can be informative of psychological problems in stroke generally. I have provided statistics indicative of prevalence rates of important pre-stroke conditions and investigated possible risk factors that were previously unstudied or inconclusive in their proposed association. The information I have established should help in understanding the natural history and aetiology of psychological problems in stroke, but more work of this kind is still needed.

I also conducted a number of studies designed to improve assessment of the pre-stroke state. This is an area of particular significance. Pre-stroke assessment can be challenging due to the frequent practical necessity that requires it to be determined retrospectively. This general limitation however is often exacerbated by heterogeneity in approach to assessment, which is largely down to a lack of knowledge and guidance for tool selection and application. I have attempted to strengthen our understanding of the psychometric properties of various tools that can be used to assess pre-stroke conditions and looked at how they compare in this regard. Our findings should assist clinicians and researchers

alike as to optimal selection and utilisation of pre-stroke assessment tools. However, there is still considerable work required in this area—particularly in relation to the psychometric properties of the tools beyond validity. Further improving how we assess the pre-stroke state should be beneficial to the field of psychology in stroke and I would encourage more work of this nature to build upon the findings presented in this thesis.

Appendices

Appendix1: APPLE protocol

Improving our assessment and understanding of the short, medium and longer term neuropsychological consequences of stroke

Running Title:	Assessing Post-stroke Psychology Longitudinal Evaluation (APPLE)
Lay Title:	Understanding the emotional, thinking and memory problems that can follow a stroke
Protocol Version:	1.5
Date:	08.12.17
REC Reference Number:	16/SS/0105
Sponsors Protocol Number:	GN14NE496
Protocol registration:	researchregistry1018
Sponsor:	NHS Greater Glasgow and Clyde
Funders Reference:	PPA 2015/01_CS0
Funder:	Joint Stroke Association and Chief Scientist Office Programme Grant

Amendment number	Date	Protocol version
AM01	19.09.16	1.3 (GN14NE496)
AM02	22.05.17	1.4 (GN14NE496)
AM03	08.12.17	1.5 (GN14NE496)

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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Protocol Approval

Improving our assessment and understanding of the short, medium and longer term neuropsychological consequences of stroke

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ABBREVIATIONS

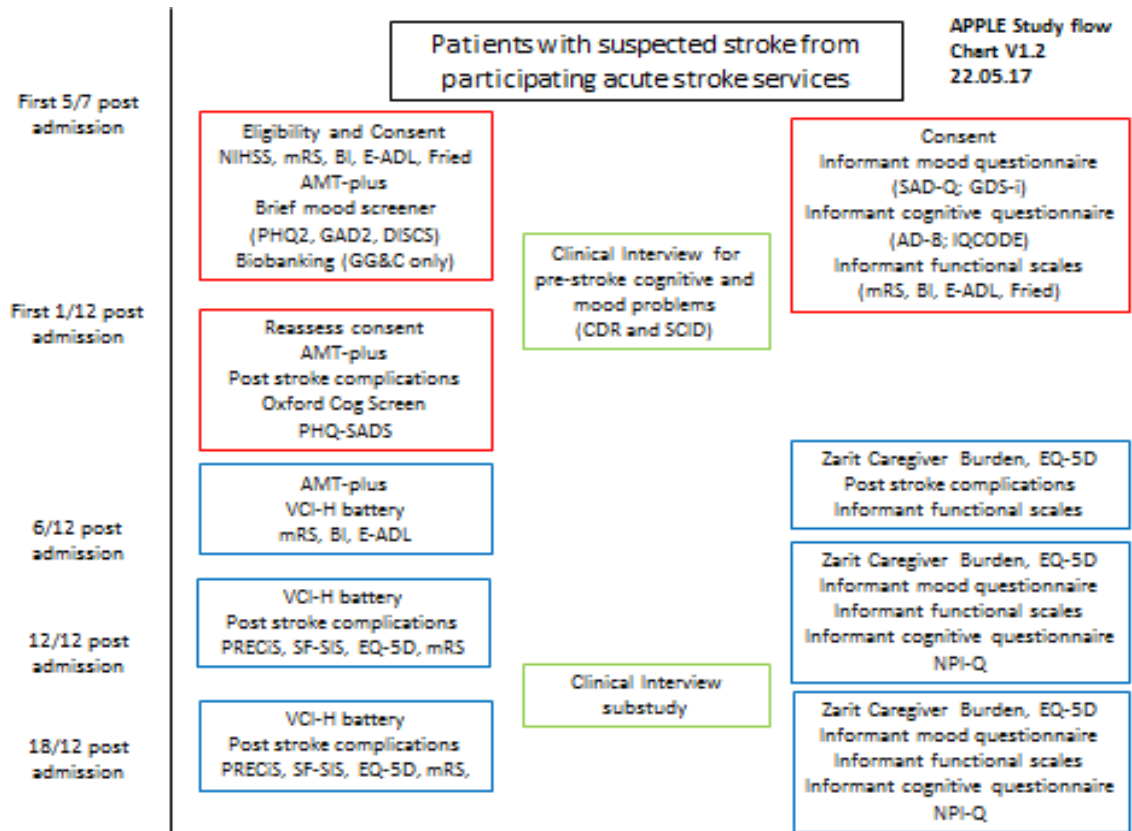
AD8	Ascertaining Dementia 8 Question Screener
AE	Adverse Event
AMT	Abbreviated Mental Testing
ASU	Acute Stroke Unit
BI	Barthel Index
CAM	Confusion Assessment Method
CDR	Clinical Dementia Rating
CRF	Case Report Form
DISCS	Depression Intensity Scale Circles
DSM	Diagnostic and Statistical Manual of Mental Disorders
E-ADL	Extended Activities of daily living
EQ-5D	Euro-QOL 5 Dimensions
GAD-2	Generalised anxiety disorder (2 question screener)
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
IQCODE	Informant Questionnaire Cognitive Decline in the Elderly
MCN	Managed Clinical Network
mRS	Modified Rankin Scale
NE-ADL	Nottingham Extended Activities of Daily Living
NIHSS	National Institutes of Health Stroke Scale
NPI-Q	Neuropsychiatric Inventory Questionnaire
OCS	Oxford Cognitive Screen
PHQ-2/SADS	Patient Health Questionnaire (2 question screener) (structured assessment)
PI	Principal Investigator
PIS	Patient Information Sheet
PRECiS	Patient Reported Evaluation Cognitive Impairment Scale
QEUH	Queen Elizabeth University Hospital
RAH	Royal Alexandra Hospital
SADQ-10	Stroke Aphasia Depression Questionnaire
SCID	Structured Clinical Interview for DSM
SF-SIS	Short Form Stroke Impact Scale
SOP	Standard Operating Procedure
SRN	Stroke Research Nurse
SSRN	Scottish Stroke Research Network
STARD	Strengthening Transparency and Reporting in Diagnostic Studies
TIA	Transient ischaemic attack
VCI-H	National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards
WP	Work Package

STUDY SYNOPSIS

Title of Study:	Improving our assessment and understanding of the short, medium and longer term neuropsychological consequences of stroke
Study Centre:	Glasgow Royal Infirmary and associated hospitals of the Managed Clinical Network for Stroke or Stroke Research Network.
Duration of Study:	4 years
Objectives:	To establish a prospective inception cohort, recruited early after stroke and followed for up to 18 months with a focus on psychological outcomes.
Primary Objective:	There are three distinct work packages (WP). WP 1. To assess the prevalence of psychological problems that pre-date stroke. (A separate complementary study will describe test accuracy of short questionnaires for assessing pre-stroke psychological problems). WP 2. To assess test accuracy and utility of brief cognitive and mood tests short for assessment of short and longer term psychological outcomes. WP 3. To describe change in cognition and mood over time following a stroke, with assessments at one, six, twelve and eighteen months.
Secondary Objectives:	The secondary objective is to create a resource that can be used for future studies of psychological impact of stroke. To this end we will ask participants if they wish to have blood taken for biobanking; if we can hold their anonymised data (clinical, laboratory and radiological) in a secure database and if we can access de-identified data from electronic health records.
Main Study Endpoints	Pre-stroke cognitive and physical function (based on CDR and SCID structured interviews). Change in cognition or mood symptoms based on repeated neuropsychological assessment (using VCI Harmonization Standard). Development of incident cognitive or mood disorder (consensus agreement based on collected materials).
Rationale:	National stroke guidance recommends early cognitive and mood screening but this policy lacks evidence-base. Building on previous work, we will create a programme of research designed to inform practice and policy. We will major on themes of "natural history" of neuropsychological problems; screening test accuracy/feasibility; prognosis and user experience.
Methodology:	Prospective, observational cohort with nested test accuracy studies.
Sample Size:	500 participants recruited to primary study, with plans for pooled analyses with other studies. Attrition is expected and we have based sample size on 200 participants completing 18 month assessments.

	The pre-stroke assessment diagnostic study is based on a separate sample size calculation and requires 100 informant interviews and diagnostic assessments.
Screening	Case note review of in-patient / outpatient attendees to the Acute Stroke Services by clinicians. A full log will be maintained.
Inclusion Criteria	<ol style="list-style-type: none"> 1. Clinical diagnosis of stroke or transient ischaemic attack (TIA) at time of assessment. 2. Age greater than 18 years. 3. Treating clinician happy that the patient would have some form of psychological assessment as part of usual care.
Exclusion Criteria	<ol style="list-style-type: none"> 1. Non-stroke diagnosis at time of assessment. 2. Unable to consent and no suitable proxy available. 4. No spoken English pre-stroke. 4. Prisoners.
Statistical Analysis	<p>WP 1,2: Accuracy of screening tools will be described in terms of usual test accuracy metrics against a reference standard of semi-structured baseline clinical assessment (WP1) or prospective assessment with neuropsychological battery (WP2). We will employ an "intention to diagnose" approach.</p> <p>WP 3: Outcomes of interest are change in scores on neuropsychological battery and incident clinical mood disorder or cognitive impairment.</p> <p>We will use generalized linear models for prospective data to describe associations of baseline characteristics with change across repeated neuropsychological measures and use varying competing risk survival models. We will describe univariate and adjusted independent predictors of "outcomes" using odds-ratios for binary "outcomes" at chosen time-points. We will create prognostic models and if data allow predictive risk scores for outcomes, describing calibration; discrimination and validation using bootstrapping.</p>

STUDY FLOW CHART



NB. All aspects of the study are optional, participants can chose to contribute to all or only one part of the study. Some sites may not be able to offer biobanking.

Key: Red boxes: short screening assessments; blue boxes: detailed screening assessments; green: structured psychology assessment with clinician input.

Details of all the neuropsychological battery assessments in appendix.

PARTICIPANT SCHEDULE

Detailed Participant Schedule					
	ASU	Follow up			
	Week 1	1 month	6 months	12 months	18 months
Review Eligibility	√				
Consent	√				
Blood / Urine for Biobanking (separate optional study)	√	√	√	√	√
Patient assessment	√				
Informant assessment	√				
Structured clinical interview study (separate optional study)		√			
Consent re-assessed		√			
Patient psychological screen		√			
Patient neuropsychological battery			√	√	√
Informant questionnaires			√	√	√
Clinical assessment (separate optional study)					√
Consensus assessment					√

NB. All aspects of the study are optional, participants can chose to contribute to all or only one part of the study. Some sites may not be able to offer biobanking.

1 INTRODUCTION

1.1 Background

We propose a programme of work designed to improve our understanding of neuropsychological effects of stroke. We will focus on themes of assessment, prognosis and natural history. Outputs will have immediate relevance and impact, providing an evidence base to policy and practice around early cognitive and mood screening and informing the design and conduct of future studies. The prospective cohort and biobank/big data resources created through this work will act as foundation for an ongoing portfolio, creating cross institutional research synergy; encouraging new researchers and providing the “substrate” for ongoing interdisciplinary work.

People affected by stroke have consistently highlighted the importance of neuropsychological issues.[1] However, the field remains relatively under researched. Important evidence gaps collated at a Stroke Association convened priority setting workshop, were around the “natural history” of neuropsychological change after stroke; utility of early assessments and predicting who will require later specialist input.[2] Our proposed body of research is designed to address these priority areas. Specifically, we will create a “real world” acute stroke inception cohort, offering prospective cognitive and mood testing to progress inter-related themes (Work Packages). We will also offer related complementary, optional studies looking at pre-stroke assessment and facilitating biobanking and ‘big data’ approaches.

Despite the importance of psychological issues, memory, thinking and mood have not received as much attention in stroke research as other areas.[3,4] For this reason there are still fundamental questions that we don’t know the answer to. These include:

- How do memory thinking and mood change after stroke?
- What happens to memory, thinking and mood in the longer term after stroke?
- Can we predict which people will have problems with memory, thinking and mood?
- What is the best way to look for problems with memory, thinking and mood?
- When should we perform tests of memory, thinking and mood?

These are the questions we wish to answer with this programme of research.

1.2 Pilot data to support the creation of a cohort

The proposed programme of work builds on our previous systematic review and original research. Our national questionnaire and literature review has shown inconsistency in neuropsychological assessment strategies both in clinical practice and in research.[3,4] Subject responses from stroke units across Scotland suggest that clinical teams are looking for guidance around method and timing of neuropsychological assessment and around prognosis.

Our systematic review work has highlighted a lack of data around cognitive and mood screening tools in acute care, albeit this is where the majority of initial assessment is performed.[5]

With the Standards for Reporting of Diagnostic accuracy in Dementia (STARDdem) working group, we have creating guidance for conduct and reporting of diagnostic test accuracy studies and have used this to inform the proposed work.[6]

Importantly, our pilot work has shown that studies of early neuropsychological assessment with prospective follow up can recruit rapidly and efficiently.[7,8]

1.3 Involvement of stroke-survivors and others affected by stroke

This body of work has been created with input from stroke survivors and others affected by stroke. Input from stroke survivors and those affected by stroke will continue for the lifespan of the study.

The researchers involved in this application were part of a national research priority setting group that collated feedback from various groups including strong representation from stroke survivors and care-givers. The number one research priority identified through this work was around problems with memory and thinking that can occur after stroke. This feedback was the inspiration behind this work.[1]

The Stroke Association ran their own workshop around memory and mood problems, the lead applicant in this work was part of this group, that also included stroke survivors and representation from various professional groups. The conversations and experiences shared as part of this workshop and our daily clinical work in stroke units helped us create a body of work that we believe is relevant to stroke survivors and is in keeping with the issues that they feel are important. The project was further reviewed by Stroke Association lay members as part of the grant review process.

The research plan outlined in this application has been previously assessed by panel members of the UK Stroke Research Network CSG (acute and rehabilitation groups). This group includes clinicians from various disciplines and representation from those affected by stroke. The insightful suggestions and comments we received, particularly around the conduct and reporting of the work, have improved the proposal considerably.

In designing a study, researchers always need to balance their desire to collect detailed information with not over-burdening the person taking part in the study. With a stroke group based in Edinburgh we have shared the various tests of memory, thinking and mood that we propose to use. Feedback from the group helped us refine our set of tests to a selection that should be acceptable to stroke survivors while still giving us the necessary information we need to answer our research questions.

As part of the study we will create an advisory group, who will meet once yearly. The advisory group will include two stroke survivors as well as representation from doctors, nurses and therapists. The group will act as a forum for stroke survivors and others to comment on the design of the study; the progress of the study; the "meaning" of the results obtained and how to share these results with the wider stroke community including stroke survivors. (*advisory group members detailed in appendix*)

1.4 Principal research questions

This application is towards a programme of work supported by the Stroke Association and Chief Scientist Office Scotland.

Within the programme are three distinct work packages (WP) designed to offer rich data that answer a number of important questions in stroke care.

WP 1. The primary aim is to assess the prevalence of memory and thinking (cognitive) and mood problems that pre-date the stroke. A complementary (optional) study seeks to describe the test accuracy of short questionnaires for assessing pre-stroke psychological problems.

WP 2. The primary aim is to assess how useful short tests are for detecting cognitive and mood problems immediately after a stroke and for detecting persisting cognitive and mood problems.

WP 3. The primary aim is to describe change in cognition and mood over time following a stroke, with assessments at around one month, six months, twelve months and eighteen months.

A further important objective is to create a resource that can be used for future studies of psychological impact of stroke. To this end we will ask participants if they wish to have blood taken for biobanking (optional); if we can hold their anonymised clinical, laboratory and imaging data in a secure database (optional) and if we can access de-identified data from electronic health records (optional). All these aspects are optional and may not be available in certain centres.

1.5 Summary of Risk Assessment

We recognise the potential issues associated with this project; we have worked with patient groups, lay representatives and clinical study advisory groups to create a methodology that minimises issues while maintaining the research potential of the programme of research. We have listed the potential issues and steps taken to minimise their impact.

Test burden: The project involves cognitive and mood testing of patients and informants at various stages in the stroke journey. We recognise the importance of minimising test burden. Our pilot work suggests that patients struggle with standard, multidomain cognitive tests in the first days post stroke. In this study we will concentrate on very brief tests. As the brief tests share a number of questions, we can assess the performance of several tests at once by simply adding some questions to the short cognitive assessment that is used as standard in our clinical service.

As part of our preparatory work we asked a stroke group based in Edinburgh to look at the tests we proposed for the acute study and they were happy that the tests were not overly burdensome. Piloting the acute test battery with an Edinburgh research group suggests that completion should take around 20 minutes at most. Patients are not required to complete all the tests and they can ask to stop testing at any time. Testing can be performed in two sessions or more depending on patient preference. Feasibility of using brief tests is an important metric of this work and we will record how many patients attempt and complete tests. If a participant becomes distressed or frustrated and it is clear that they are unable to complete testing, testing will be stopped. Any distress will be handled through reassurance and ending the assessment.

Informants (family, friends, carers) will also be asked to complete paper based questionnaires. We have chosen brief assessments that should take around 20 minutes and can be completed at a time that suits the participant.

The prospective arm of the study will use a longer test battery. Completing the study follow-up will involve four assessment visits over 18 months (one month; six months; twelve months; eighteen months). We have chosen cognitive and mood tests recommended for stroke cohorts and which we use in clinical practice. There is considerable experience of using these tests with stroke survivors. The first session using these longer test batteries will not begin before six months post stroke to allow time for recovery. Again testing can be performed in split sessions if the patient prefers. Completion of the tests is not mandatory and the patient can request to stop testing at any time. Where completion of the full assessment is not possible, we have specified a short form assessment protocols for use in person or over telephone.

Opportunity cost: We recognise that while a patient is working on cognitive assessment they will not be able to work with ward staff / allied health professionals on other rehabilitation tasks. We will work with the ward team to minimise disruption. We will be performing an activity, cognitive and mood testing screen, that is a recommended part of routine care. We will share the inpatient test results with ward staff on request and this should release their time for other activities.

Disclosure of sensitive information: We will be assessing mood (emotions and feelings) we recognise that this can be a sensitive area. If we detect probable depression, or other mood disorder we would advise the clinical team to refer to the Stroke Psychology service. In the event that suicidal thoughts/ideations are disclosed assessment will be stopped and a member of the treating clinical team will be informed immediately. This action will also be documented in the patient's case notes. The study

has input from the local Clinical Stroke Psychology service and they are happy to be contacted in the event of suicidal ideation or any other disclosures that may require clinical input.

Patients may ask for their scores on the cognitive or mood tests. We will share these data with the patient but we will also explain that these tests in and of themselves are not diagnostic of dementia / depression or other serious psychological problems. Rather they are part of an assessment that will be shared with the treating clinical team. If there is concern regarding a patients cognitive function or mood, the research team can access the stroke clinical psychology services and referrals can be made to Memory Clinic services.

Informed consent: We want our study to produce results that reflect “real world” stroke care. Previous studies of cognition and mood in stroke have limited themselves to consenting patients. This gives a biased sample and produces results that lack external validity and clinical utility. We propose a more generalizable approach, where we potentially include all patients with stroke unless the clinical team feel that any form of testing is inappropriate. There will be a proportion of patients who may struggle to provide informed consent to research. For a study with a cognitive focus, it is important that these patients are included. In this instance we will seek consent from a suitable proxy (family, friend, carer). For those patients who are included in the study with proxy consent; we will reassess capacity to consent and seek informed consent at one month follow-up visit.

Test environment: For follow-up testing we will recommend that testing is performed within one of the clinical research facilities of the participating hospitals. We have a budget to cover patient travel by taxi to allow this. Some patients may be unable to attend the research facility or may for any reason choose to be assessed at home. Telephone based assessment is possible if required. For home assessments, we will follow NHS GG&C and GU lone working procedures for safety.

Use of participant data: Our cohort will provide a unique resource for understanding post-stroke psychological problems. We wish to maximise the potential of the data collected, so that it can be used to answer clinically important questions beyond those outlined in the primary study. Certain centres will invite participants to give a blood samples that will be stored for future analyses. Participants can decline this biobanking aspect at any stage of the study and still help with other aspects. The Robertson Centre for Biostatistics will hold anonymised patient data within a secure resource. Our study follow-up is limited to eighteen months. We will ask participants permission to link their study data to anonymised data from electronic health-records (clinical, laboratory, imaging). This will allow future studies to look at longer term outcomes. Again, participants can chose to decline this aspect of the study but contribute to the other aspects.

2 STUDY OBJECTIVES AND PURPOSE

We propose a study that has been designed to answer pressing clinical questions. National and international stroke guidelines recommend early cognitive and mood screening but this policy is based on expert opinion and lacks evidence-base. Building on our previous pilot work, we will create a programme of research designed to inform practice and policy. We will major on themes of "natural history" of neuropsychological problems following stroke; screening test accuracy/feasibility and prognosis.

We anticipate that at study completion we will be able to offer:

- Guidance on the optimal methods to assess for pre-stroke cognitive and mood problems.
- Guidance on the optimal methods to assess for cognitive and mood problems in the acute stroke setting and in early follow-up.
- Descriptions on the natural history of cognitive and mood symptoms following stroke.
- An understanding of clinical, demographic features that predict poor and good psychological outcomes following stroke.

STUDY DESIGN

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended). All investigators and key study personnel will undergo biennial GCP training.

The study design is detailed below and is summarised in the flow chart and schedule.

The programme of work is based on a prospective observational cohort, recruited at time of stroke and followed up with assessments focussing on neuropsychological aspects. The cohort will allow for studies of test properties, studies of prognosis and epidemiology. Inclusion of a biobank and consent to future electronic data linkage increases the research potential of the cohort.

3.1 Study Population

The study will involve participants aged over 18 years with clinical diagnosis of stroke or transient ischaemic attack (TIA) who meet the inclusion criteria and have none of the specified exclusion criteria. All will give full informed consent or have consent provided by appropriate proxy.

Participants will be consecutive, stroke patients over 18 month recruitment. Primary sites will be Glasgow Royal Infirmary (GRI); Royal Alexandra Hospital (RAH) and Queen Elizabeth University Hospital (QEUH), with additional recruitment from other Scottish Stroke Research Network (SSRN) sites or research active stroke centres in other parts of the UK. To allow descriptions of generalizability and feasibility we will adopt an inclusive policy, offering testing to all adult (over 18 years) stroke survivors except where clinical team feel that any form of testing is inappropriate (for example end of life care). We will define stroke using World Health Organisation criteria. Our stroke rubric will include TIA and minor stroke and recruitment from outpatient clinics will be possible. Co-recruitment with other observational or investigational trial will be possible.

We will include patients with varying levels of communication problems. Our national ethics application will allow us to seek proxy consent for assessment and follow up where participant is unable to give direct consent at time of recruitment. The context is disease orientated and so will include new TIA/minor stroke seen at clinics as well as inpatients. Eligibility screening and recruitment will be performed by stroke research nurses or trained researchers. Initial assessment of capacity and willingness to be approached will be determined by the clinical team.

3.2 Main Study Inclusion Criteria

1. Clinical diagnosis of stroke or TIA at time of assessment
2. Age greater than 18 years.
3. Clinical team happy that patient is suitable for some form of psychological testing.

Stroke will be diagnosed by a stroke specialist, defined as a focal neurological event of presumed vascular cause. We will operate no time or imaging based inclusion criteria.

3.3 Main Study Exclusion Criteria

1. Non-stroke diagnosis at time of assessment.
2. Unable to consent and no suitable proxy available.
4. No spoken English pre-stroke.
4. Prisoners.

3.4 Description of the work packages

We propose a programme of work themed around improving cognitive and mood assessment.

The portfolio is described as interlinked work-packages each with distinct aims and objectives. In addition we offer optional, complementary studies.

Work package one: Assessing pre-stroke psychological problems.

- To describe prevalence of pre-stroke psychological problems (specifically, cognitive decline and depression) in an acute stroke cohort.
- A separate (optional) study will assess the feasibility of using informant based screening tools for pre-stroke depression (GDS-informant scale; SADQ-10) and cognitive decline (IQCODE, AD-8) in an acute stroke setting.
- A separate (optional) study will assess the accuracy of informant based screening tools for pre-stroke depression (GDS-informant scale; SADQ-10) and cognitive decline (IQCODE, AD-8) against a reference standard of semi-structured clinical assessment (using the Structured Clinical Interview [SCID] for DSM mood disorder and the clinical dementia rating [CDR] for cognitive assessment).

Published research describing cognitive and mood problems following stroke assumes that the person had no problems prior to the stroke event. This is overly reductionist approach fails to appreciate the complex relationship between psychological symptoms and cerebrovascular disease. Stroke is predominantly a disease of older age and older people will show varying degrees of cognitive decline and mood problems. These may be sufficient to warrant a diagnostic label, albeit often a diagnosis of dementia or mood disorder is not made in the community.[9] Both cognitive decline and mood disorder seem to be associated with increased risk of stroke.[10]

To understand the psychological picture seen after stroke we need robust methods of capturing the pre-stroke state. A common approach is to conduct a questionnaire based interview with informants (family, friends, carers) and use the description of past cognitive and mood symptoms to assign a retrospective label. Scales are available and are used in stroke care, for example the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE). Our recent systematic review has shown that while test properties of informant scales are good in community dwelling older adults, no informant questionnaire has been validated in a stroke population.[11,12]

We will use a classical test accuracy study design to describe the properties of informant tools in acute stroke. Stroke research nurses (SRN) or trained researchers will interview informants with short questionnaires looking to describe pre-stroke depression and cognition. Within one month of this assessment, a trained member of the research team will conduct a semi-structured interview (based on standardised questionnaires of SCID and CDR (sum of boxes scoring <https://www.alz.washington.edu/cdrnacc.html>) with patient and family and formulate a clinical assessment of pre-stroke problems. Following discussion with a clinician, results will be operationalised as pre-stroke dementia or depression probable; possible; unlikely; unable to assess.

Accuracy of screening tools will be described in terms of sensitivity; specificity; predictive value; receiver operating space analyses. Index test questionnaires will be compared against each other and against a reference standard of semi-structured clinical assessment. To describe feasibility we will collate numbers completing each test fully and partially; time and assistance required for completion. To incorporate feasibility into analyses, we will employ an "intention to diagnose" approach, including those unable to complete tests.[13]

Work package two: Test accuracy and prognostic utility of brief screening tools

- To describe feasibility of using brief screening tools for diagnosis of cognitive and mood problems in acute stroke.
- To describe accuracy of brief screening tools for diagnosis of cognitive and mood problems in acute stroke; comparing to each other and to a one month multi-domain assessment.
- To describe prognostic accuracy of a one month multi-domain cognitive and mood assessments against detailed assessment at six, twelve, eighteen months.
- To describe neuropsychological "case-mix" with reference to incident/prevalent delirium and impairments that may complicate cognitive and mood testing.

The first step to management of neuropsychological problems is recognition and diagnosis. At present we have no agreed method on how or when to assess for these problems. Our pilot data suggests that standard multi-domain assessment tools are not feasible as a universal screen in the first days post stroke.[5,8] Thus, we suggest a neuropsychological assessment paradigm where brief assessments are used in the hyperacute period with increasingly detailed assessment at later time period.

Various brief (less than five minutes) assessment tools for cognition and mood are available. Such tools are suited to acute settings and indeed are often used in the ASU, however data on test properties are limited.[5] Many of these brief assessments have shared items. We have created an instrument that combines elements from popular brief tests in a single assessment, allowing derivation of various scores while minimising test burden. Our brief mood testing includes a depression and anxiety questionnaire; pictorial assessment and single question. Tests for delirium are also included. We have not modified assessments for those with communication problems, as describing feasibility of tests across a range of stroke related impairment is an important outcome of our work. However, the tests used should be feasible for those with mild to moderate aphasia. At one month, a longer test battery will include multi-domain screening tool. (Assessments described in appendix).

Our methodology is based on best practice in conduct and reporting guidance for dementia test accuracy studies (STARDdem).[6] Index test will be brief screening tools (acute assessment) and multi-domain screening tools (one month and beyond). Given the dynamic early changes in cognition and mood seen early after stroke, purpose of early testing should be to predict later problems. Thus our reference (gold) standard comparator will be mood disorder and multi-domain cognitive impairment as described by our neuropsychological battery at six, twelve and eighteen months with expert consensus diagnosis based on all collated materials at end of study. We recognise that these assessments are not diagnostic, rather they offer a suitable compromise between validity of assessment and suitability post stroke where formal diagnosis of dementia or mood disorder can be challenging. As an optional study, at 12/12 and 12/18 follow-up a random selection of participants, will be offered additional face to face clinical assessment with a senior stroke neuropsychologist or clinician blinded to other assessment scores. At completion all 6,12,18 month study materials will be reviewed by the senior investigators (TQ, NB, JD, DJS) and a consensus diagnosis assigned for incident mood disorder and/or incident cognitive disorder, using descriptors of: probable, possible, unlikely.

Accuracy of screening tools will be described in terms of sensitivity; specificity; predictive value; receiver operating space analyses. Index tests will be acute and one month assessments and will be compared against each other and reference standard of follow up assessment data. From the acute assessments, we will describe the accuracy of brief screening tests used in isolation and combined with Boolean operators of "OR"/"AND". To describe feasibility we will collate numbers completing each test fully and partially; time and assistance required for completion. To incorporate feasibility into analyses, we will employ an "intention to diagnose" approach, including those unable to complete tests.[13]

Work package three: Describing and predicting neuropsychological prognosis

- To describe serial change in cognition/mood test scores and to describe prevalence of cognitive and mood diagnoses at time points of one month; six month; twelve months and eighteen months.
- To describe univariate and adjusted independent predictors of both post stroke cognitive decline and post stroke mood disorder.
- To develop, calibrate and validate predictive models for post stroke neuropsychological factors.
- To estimate likely recruitment, "event rates" and loss to follow up for future cognitive/mood studies.

Systematic reviews suggest substantial post stroke neuropsychological burden, however these data may have limited generalizability to acute settings.[14] Problems include selection bias; non-acute sampling and lack of data on important comorbidities such as delirium and prevalent dementia. Our pilot data describes a high incidence of cognitive/mood problems in first days post stroke with trajectories of improvement, stabilisation and decline.[8] We need "real world" data on baseline and natural history of neuropsychological change to inform practice, research and policy in this regard.

Follow up will be at six, twelve and eighteen months, time-points chosen to reflect common clinical and study assessment times. Assessments will be face-to-face and performed in study centres or in participant's home as required/requested. There will be opportunity for telephone assessment if required. The six/twelve/eighteen month assessments will be performed by trained members of the research team. We make no assumptions around the pathology underlying post stroke cognitive change and so we have devised a battery of assessment that will allow derivation of scores for "vascular" dementia and Alzheimer's Disease dementia.[15,16] While our principal mood interest is depression we have chosen a mood assessment that screens for various other disorders using structured clinical interview.[17] (see appendix for full details of all assessments) After 12 and 18 month follow-up, a proportion of participants will be asked if they wish to take part in an optional study, where they are assessed by a clinician and assigned a clinical label. These results will be compared to our standard assessments.

The work is modelled around the "fundamental" prognosis research paradigm as described by MRC PROGRESS prognosis research group.[18] Taking acute stroke as start-point, we will create an inception cohort, collecting clinical, demographic and neuropsychological "phenotyping" data at baseline and then prospectively following up with serial cognitive and mood assessments.

For prospective follow up, outcomes of interest are change in scores on cognitive and mood screening tools and incident clinical mood disorder or multi-domain cognitive impairment. Multi-domain tools will be analysed as ordinal data and dichotomised at varying thresholds. Neuropsychological battery data will be transformed into z scores, with impairment defined as greater than 1.5 standard deviations below age and sex based norms. We will collect data on recurrent stroke, complications (falls, seizure, infection) hospitalisation/institutionalisation and death.

We will explore repeated measures analyses adjusting for baseline covariates and describe temporal change in test scores. We will create prognostic models and if data allow predictive risk scores for the various cognitive and mood outcomes, describing calibration; discrimination and validation using bootstrapping.

3.5 Identification of Participants and Consent

Potential participants will be identified (by clinical or case note review by a member of the clinical team or attending Doctor) whilst in-patients or in a cerebrovascular out-patient clinic. If the patient asks not to be approached no further action will be taken. The clinical team will make an assessment of capacity to consent to inclusion in the study. The principal criterion for entry into the study is that the treating team believe

an attempt at cognitive and mood assessment is appropriate. We have used this approach in previous pilot studies and it has worked well.

Following identification, potential participants will be approached in person and asked whether they would wish to consider taking part in the trial. Those who are willing to hear more will be given the participant information sheet (PIS) and a date (at least 24 hours later) arranged for further discussion with a member of the research team. Eligibility will be confirmed by an investigator.

At this second meeting, subjects will be asked if they have any questions and those who wish to participate will be asked to sign the consent form. Two copies will be signed (one each for the participant and the site file) and a copy of the signed consent form will be inserted into the casenotes.

Consent will be taken by one of the investigators, research nurse or trained researcher.

Consent will be staged to ensure that participation in the study is always voluntary and fully informed. At all points we will stress that taking part in the study is voluntary and if patients wish to terminate the cognitive testing early we will respect this wish which will not impact on the clinical care that they receive.

For patients unable to provide informed consent, we will seek consent from a legal proxy or family, carer, friend. We have outlined the details of this approach in the section on adults lacking capacity (see below).

We offer additional complementary studies looking at informant assessment; blood taking for biobanking; prospective follow-up; clinical diagnostic study; data storage and linkage. Participants will be given the option to consent to all aspects of the study or to limit their participation to certain aspects only. In centres where biobanking is not possible this will not be included in consent form.

We recognise that cognition can change over time. Our pilot data suggests that immediately after stroke patients can have cognitive impairments that improve over the first weeks.[8] At early follow-up (around 4 weeks post stroke) the participant's capacity to consent will be reassessed.

3.5.1 Including participants unable to provide informed consent

We wish to include a representative sample of stroke survivors. For a study that is concerned with post stroke psychological problems we need to include a spectrum of cognitive abilities and impairments. Previous work in this area has been limited by including non-representative populations and so results have lacked real world validity. To ensure our results have clinical utility, we will be maximally inclusive in our recruitment strategy.

Patients may have cognitive problems, problems with communication/language or physical impairments. Some may have severe communication or cognitive difficulties. The assessment battery we propose, while not specific to aphasia, should be suitable for those with mild to moderate communication problems. We will only assess those patients where the clinical team feel that an attempt at assessment of mood or cognition is appropriate.

We do not wish to deny stroke survivors involvement in a study that might lead to benefit for those like them. We believe the risk of participation in this observational study is minimal.

Decisions on patient capacity to consent will be made by the Consultant/senior members of the Acute Stroke team at daily ward rounds or on first assessment. This is a standard part of usual clinical practice for stroke clinical teams.

Where the ward clinical team determine a patient does not have capacity to consent, we would seek informed consent from a close relative/welfare guardian. We would still include the patient in decision making around the study as possible. Choice of proxy will be made by the patient, either at the time of testing or based on previously expressed wishes.

We will involve the nearest relative/guardian/welfare attorney in the study, regardless of patient ability to consent as some of our measures require to be completed by an informant that knows the patient well. We have developed a specific information leaflet (PIS) for this purpose.

Capacity to consent will be re-assessed at one month follow-up. If a patient has been included using proxy consent but it is felt the patient now has capacity, consent will be rechecked at the follow-up visit. In this scenario, if the participant does not give consent the participant would be withdrawn from the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant. We would ask if those identifiable data or tissue already collected with consent could be retained and used in the study. If the participant does not agree to this, the data and biobank samples will be removed from study registers.

If the patient is felt to no longer have capacity to consent, the assessor will follow procedures outlined for including a patient that lacks capacity. In this scenario, if a relevant proxy does not give consent the participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

At subsequent follow-up visits, capacity to consent will not be formally reassessed but we will check that the participant is still happy to continue with the study and emphasise that the participant can withdraw at any time and not give a reason

3.5.2 Withdrawal of subjects

Participants will be told that they can withdraw their consent at any time without giving a reason and that this will not affect their care in any way. Participants will be informed that they can participate in any or all of the follow up assessments.

3.6 Assessment Schedule

The study will comprise a maximum of seven patient assessments. A short baseline assessment; (optional) semi-structured clinical interview within first month; one month follow-up with short screening tests; then six, twelve, eighteen month follow-ups with multi-domain assessments with an optional clinical diagnostic assessment. Following the baseline assessments, each visit has a two week time window either side of the scheduled date during which it can be completed. Other than baseline assessment, assessments will be preferentially performed in the Clinical Research Facility of the participating hospital. There is the option for home assessment or for telephone assessment if required.

3.6.1 Baseline assessment

This will be completed as soon as possible following index stroke but not before 24 hours to allow participants sufficient time to read study materials. Initial assessment will confirm eligibility and consent. Clinical and demographic details will be extracted from case-notes. Clinical assessment will include National Institute of Health Stroke Scale (NIHSS) score, modified Rankin Scale (mRS); Barthel Index (BI): five question assessment for frailty (Fried), Lawton Extended Activities of Daily Living (E-ADL) a short questionnaire around physical activity (Brief Physical Activity Assessment [BPAA] and a measure of social inclusion (Medical Outcome Study Social Support Scale[MOSS-SSS] 4 item).

The cognitive assessment (AMT-plus) will comprise the 10 point abbreviated mental test and clock drawing test, supplemented by a recall question, one letter fluency test

and naming months of the year backwards. This battery allows us to derive the score from 9 different screening tests without performing each test individually. We will assess for delirium using Confusion Assessment Method (CAM-ICU). We will assess for mood symptoms using Depression Intensity Scale Circles (DISCS) and the short forms of Patient Health Questionnaire PHQ-2/GAD-2. If patient agrees and facility is available, bloods and urine will be taken for biobanking.

Informants will be chosen by the stroke patient or ward staff if stroke patient unable to make this decision. Informants will complete brief questionnaires describing the patient's mood and cognition pre-stroke. Questionnaires will comprise the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE); the Ascertain Dementia screener (AD-8). The Geriatric Depression Scale informant version (GDS-i) and Stroke Aphasia Depression Questionnaire (SAD-Q). Patients pre-stroke functional ability will be assessed using the BI, Fried and E-ADL. The baseline visit will confirm a suitable time to organise the semi-structured clinical interview.

3.6.1.1 Semi-structured clinical interview

This optional study interview will be performed within one month of baseline assessment. A trained member of the research team will interview the patient and informant. Interview will cover diagnostic criteria necessary to assign a label of major neurocognitive disorder; delirium and major depression. The content will be based on the operationalised structured clinical interview for DSM-5 (SCID) and the Clinical Dementia Rating (CDR – sum of boxes scoring <https://www.alz.washington.edu/cdrnacc.html>). The interviewer will not have access to previous cognitive and mood screening assessment results. Results of the interview will be discussed with the study team and a final consensus label will be operationalised as: probable cognitive/mood disorder pre-stroke; possible disorder; unlikely disorder; unable to assign a label. We will emphasise that the assessments are not diagnostic but will share the information with the treating clinical team on request.

3.6.2 One month assessment

The one month assessment will be performed at a time convenient for the patient and informant. One month assessments will comprise a repeat of the short patient cognitive battery performed at baseline (AMT-plus, CAM-ICU), the Oxford Cognitive Screen (OCS) and the complete Patient Health Questionnaire (PHQ-SADS). We will collect information on post stroke complications (stroke, cardiac, seizure, infection, falls, fatigue [using brief fatigue inventory]) and any change in medication. If the patient is agreeable and if available then further samples for biobanking will be taken.

3.6.3 Six, twelve, eighteen month visit

Assessments at six, twelve and eighteen months will be performed by researchers trained in the various assessments. Patients will be assessed according to Vascular National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards (VCI-H).[15,16] Function will be assessed with mRS, BI, EADL and BPAA, MOSS-SSS at 12 and 18 month. The patient will be asked about specific stroke complications of interest. List of medication will be updated.

At the six month assessment the assessor will use the 30 minute version of the VCI-H. If the patient struggles with this assessment, does not wish such a lengthy assessment or the assessment is not possible for any other reason, we have proposed a shorter assessment based on the VCI-H five minute battery. For twelve and eighteen month assessments the patient will be offered the choice of full VCI-H (around 45 minutes) or shorter assessments. Choice of assessment used will be at the discretion of the researcher in discussion with participant and informant.

In addition at the twelve and eighteen month visits the patient will complete generic and stroke specific quality of life measures: Euro-Qol 5 domains (EQ-5D); Short Form

of the Stroke Impact Scale (SIS) and Patient Reported Evaluation of Cognitive Status (PRECiS).

The informant will complete a caregiver burden scale (Zarit Caregiver Burden) and will complete the generic quality of life EQ-5D. At 12 and 18 months the informant will complete the cognitive and mood questionnaires employed at baseline (IQCODE, Yes include GDS-i) and will complete the neuropsychiatric inventory questionnaire (NPI-Q).

Completion of the eighteen month visit marks the end of the study.

3.7 Biobanking

Urine and blood samples will be obtained as outlined in the appendix and then will be stored in the NHS GG&C biorepository; all aspects of collection and storage will be in line with NHS Greater Glasgow and Clyde policies. Biobanking samples will be from GG&C participants only.

Venepuncture will be performed from the antecubital fossa where possible (using a ~ 19G (green needle) vacutainer (or similar) system). Three lavender top EDTA tube (or similar), a gold top clot activator (or similar) for serum chemistry measures and two grey tube (or similar) for glucose determination will be collected (ca 40 mls in total)

3.8 Team Expertise and Project Management

NHS Greater Glasgow and Clyde have agreed to act as sponsor. All protocols will be stored in publically accessible registers. Creation of case report forms (CRF), data management, archiving and analyses will be supported by Robertson Centre for Biostatistics.

Terry Quinn (Glasgow) will lead the work and act as principal investigator (PI). He has particular expertise in stroke study methodology; test accuracy and cognitive/functional assessments. The core research team will include stroke research nurses at both sites; new researcher posts, designed to allow study towards PhD and dedicated statistical support. The multifaceted nature of the topic requires knowledge and skills in various areas and our collaborators bring this multidisciplinary expertise. Our experienced site leads have international reputations for excellent multicentre, prospective research: Peter Langhorne (GRI); Kennedy Lees (QEUH). Ian Ford (Glasgow) will support all aspects of statistical analysis. Niall Broomfield (clinical lead for Glasgow stroke psychology services) will provide training for research nurses and doctoral students and will facilitate clinical assessments.

We will form an advisory group who will provide oversight and guidance, the group will have representation from stroke survivors (x2); primary care; research networks (SSRN, SCDRN); neuropsychology (Jonathan Evans, Glasgow); the local stroke managed clinical network lead (Christine McAlpine) and an external expert on neuropsychological outcomes in stroke (Sarah Pendlebury, Oxford).

4. Rater training

We propose assessments using a battery of differing neuropsychological and functional tests. We have extensive experience of training researchers in use of assessment scales. Our previous work around outcomes assessments for large clinical trials has shown the importance of offering training, standardisation and quality control, even for those tests considered "routine" in stroke research.[19]

We will use training materials produced for use with the assessments of interest. Online training resources will be available for functional outcomes (NIHSS, mRS, BI). For the neuropsychological tests we will offer face-to-face training. Educational materials will be complemented by an investigator work book and Standard operating Procedures (SOPs) for all of the assessments required in the study. To accompany

the SOPs we will create study-specific case report forms to facilitate standardised assessment and scoring. For PhD student assessors, the first three assessments will be supervised. There is scope for further direct assessment and training as required. Contact details of the principal investigator and research team will be made available to all the sites should issues arise.

5. PHARMACOVIGILANCE

We propose an observational study with no intervention or change to usual care. There are no pharmacovigilance issues specific to this work.

6 STATISTICS AND DATA ANALYSIS

6.1 Primary Outcomes

We propose a programme of inter-related projects themed around improving cognitive and mood assessment.

The portfolio is described as work-packages and optional studies each with distinct aims and objectives. The outcomes and analysis plan for each will be described in turn.

WP 1: Assessing pre-stroke psychological problems.

- To describe prevalence (n, [%]) of pre-stroke psychological problems (specifically, cognitive decline and depression) in an acute stroke cohort.
- As part of an optional, separate study, to assess the feasibility (n, [%] return rate, items complete, time for testing) of using informant based screening tools for pre-stroke depression (GDS-informant scale; SADQ-10) and cognitive decline (IQCODE, AD-8) in an acute stroke setting.
- As part of an optional, separate study, to assess the accuracy (sensitivity, specificity, positive/negative predictive value) of informant based screening tools for pre-stroke depression (GDS-informant scale; SADQ-10) and cognitive decline (IQCODE, AD-8) against a reference standard of semi-structured clinical assessment.

WP 2: Test accuracy and prognostic utility of brief screening tools

- To describe feasibility (n, [%] items complete, time for testing) of using brief screening tools for diagnosis of cognitive and mood problems in acute stroke.
- To describe accuracy (sensitivity, specificity, positive/negative predictive value) of brief screening tools for diagnosis of cognitive and mood problems in acute stroke; comparing to each other and to a one month multi-domain assessment.
- To describe prognostic accuracy (sensitivity, specificity, positive/negative predictive value, ROC analyses) of a one month multi-domain cognitive and mood assessments against detailed assessment at six, twelve, eighteen months.
- To describe neuropsychological "case-mix" with reference to (n, [%]) prevalence of pre-stroke cognitive decline; pre-stroke mood disorder (depression) and incident/prevalent delirium.

Work package three: Describing and predicting neuropsychological prognosis

- To describe the natural history (rates of outcomes; change over time) of post stroke neuropsychological problems at time points of one month; six month; twelve months and eighteen months.

- To describe univariate and adjusted independent predictors of both post stroke cognitive decline and post stroke mood disorder (odds ratios, with corresponding 95% confidence intervals).
- To develop, calibrate and validate predictive models for post stroke neuropsychological factors.
- To estimate likely recruitment, "event rates" and loss to follow up for future cognitive/mood studies.

6.2 Statistical Analysis Plan

The study will have a comprehensive Statistical Analysis Plan (SAP), which will govern all statistical aspects of the study, and will be authored by the Trial Statistician. Full details of all statistical issues and planned statistical analyses will be specified in the SAP which will be agreed before analyses begin.

6.3 Overview of statistical analysis

6.3.1 WP1: Assessing pre-stroke psychological problems

Accuracy of screening tools will be described in terms of sensitivity; specificity; predictive value; receiver operating space analyses. Index test questionnaires will be compared against each other and against a reference standard of semi-structured clinical assessment. From the acute assessments, we will describe the accuracy of brief screening tests used in isolation and combined with Boolean operators of "OR"/"AND". To describe feasibility we will collate numbers completing each test fully and partially; time and assistance required for completion. To incorporate feasibility into analyses, we will employ an "intention to diagnose" approach, including those unable to complete tests.

6.3.2 WP2: Test accuracy and prognostic utility of brief screening tools

Accuracy of screening tools will be described in terms of sensitivity; specificity; predictive value; receiver operating space analyses. Index tests will be acute and one month assessments and will be compared against each other and reference standard of follow up assessment data. From the acute assessments, we will describe the accuracy of brief screening tests used in isolation and combined with Boolean operators of "OR"/"AND". To describe feasibility we will collate numbers completing each test fully and partially; time and assistance required for completion. To incorporate feasibility into analyses, we will employ an "intention to diagnose" approach, including those unable to complete tests.

6.3.3 Work Package three: Describing and predicting neuropsychological prognosis

For prospective follow up, outcomes of interest are change in scores on cognitive and mood screening tools and incident clinical mood disorder or multi-domain cognitive impairment. Multi-domain tools will be analysed as ordinal data and dichotomised at varying thresholds. Neuropsychological battery data will be transformed into z scores, with impairment defined as greater than 1.5 standard deviations below age and sex based norms. We will collect data on recurrent stroke, complications (falls, seizure, infection) hospitalisation/institutionalisation and death. All data from 6,12,18 month assessments will be assessed by a panel of the senior investigators and a consensus assessment for incident mood disorder and incident cognitive disorder made.

We will use generalized linear models for prospective data to describe associations of baseline characteristics with change across repeated neuropsychological measures. With our statistician we will use varying competing risk survival models to account for events that may precede our neuropsychological outcomes of interest (mortality).

We will describe univariate and adjusted independent predictors of “outcomes”. We will describe odds-ratios for binary “outcomes” at chosen time-points, using multivariate Poisson regression.

We will explore repeated measures analyses adjusting for baseline covariates and describe temporal change in test scores. We will create prognostic models and if data allow predictive risk scores for the various cognitive and mood outcomes, describing calibration; discrimination and validation using bootstrapping.

6.4 General Considerations

In general we will apply parametric statistical methods; any variable not suitable for parametric analysis will be analysed using non-parametric methods.

Descriptive statistics by study centre will be provided. A summary and listing of patients with protocol violations will be produced.

6.5 Software for Statistical Analysis

All statistical analysis will be performed using SAS version 9.1 or later.

6.6 Sample Size

We anticipate recruiting $n=500$ participants across the three sites over 18 months recruitment. We expect substantial attrition (death, loss to follow-up, development of cognitive problems that preclude further assessment) and anticipate $n=400$ one month; $n=350$ six month; $n=300$ twelve month and $n=200$ eighteen month follow up data.

Data to allow sample size calculations for future studies is an intended output of this work. Recognising the uncertainty, we do not offer definitive “power” calculation per se, but our recruitment estimates suggest we will have sufficient patients to achieve our research aims.

Scottish Stroke Care Audit reports over 1500 stroke discharges per annum across our three Glasgow sites. Our pilot data suggest that over 18 month recruitment, at a conservative estimate 500 will be suitable and agree to early assessment and follow up. Based on Information Services Division stroke data, we project estimates of $n=400$ one month; $n=350$ six month; $n=300$ twelve month and $n=200$ eighteen month follow up data. These numbers make our study equivalent to or larger than other international neuropsychological focused studies. By using research nurses for initial assessments and three full time PhD student assessors for follow up, daily maximum number of assessments per team member would be two.

For the optional study describing accuracy of informant questionnaires we have a separate power calculation. Using a nomogram approach [20] describing test properties of informant questionnaires, based on estimated prevalence of pre-stroke problems of 20% and anticipated specificity of around 0.8, recruiting $n=100$ gives sufficient power to assess the scales.

WP1 and WP2. Our recruitment is designed mindful of potential attrition. For the test accuracy work, using a nomogram [20] based on prevalence of 40% cognitive impairment at one month, ($\alpha=0.05$); our estimate of 400 participants would allow description of accuracy across a full range of plausible sensitivity/specificity.

WP3. Based on published data on mood we would anticipate annual rates of outcomes at around 30% with $n=125$ “outcomes” in survivors at end of follow up (although our data suggests rates of cognitive/mood disorder may be considerably higher in unselected cohorts). This gives sufficient power for the prospective models we have

planned. Based on our anticipated recruitment and retention, prognostic models will have power to describe multiple covariates.

The optional subgroup study where results on neuropsychological assessment are compared to clinical assessment will be performed on $n=25$ in the first instance. This is a pragmatic sample size. Recruitment will be of sequential consenting participants from the Glasgow sites.

6.7 Procedures for Accounting for Missing Data

There will be no imputation of missing data for the primary or secondary endpoints in the first instance. As part of the analyses we will explore the effects of various approaches to handling missing data.

6.8 Procedures for Reporting Deviations from the Original Statistical Plan

A detailed statistical analysis plan (SAP) will be agreed before analyses begin. Any deviations from this plan will be documented and justified in the final study report.

6.9 Selection of Subjects to be Included in the Analyses

We will run analyses including those with full test data and those with missing data, using intention to diagnose approaches.

7 STUDY CLOSURE / DEFINITION OF END OF STUDY

The study will end when the last patient has their last study visit.

8 Source Data/Documents

8.1 Case Report Forms / Electronic Data Record

Primary data collection will use paper based case report form (CRF). Inpatient assessment scores will be shared with the hospital team on request. For out-patient/community assessments, screening test summary results will not be shared with the General Practitioner (GP). This approach was suggested by the Scotland A Research Ethics Committee and recognises that the screening tests are not diagnostic. If assessment suggests a serious cognitive or mood disorder that requires urgent treatment results will be shared with the appropriate team.

All participant data will be identified by the participant study identification number. CRF data will be securely transferred to the Robertson Centre for Biostatistics (RCB) for electronic entry. Data will be validated at the point of entry into and at regular intervals during the study. Data discrepancies will be flagged to the study site by the statistician and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

8.1.1 Data Handling and Record Keeping

All CRF data will be held in the RCB. The RCB manages all studies to the highest standards in accordance with its internal Standard Operating Procedures, ICH Good Clinical Practice, the European Union Clinical Trials Directive 2001/20/EC, the ICH

Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9 and all other industry legal and regulatory guidelines. It has extensive experience of managing data in the context of privacy and data protection legislature, including the Data Protection Act 1998 and EU Data Protection Directive 95/46/EC. The Centre is certified for ISO 9001:2008 for its quality systems, has TickIT accreditation for its software development and is BS7799 compliant.

Only the study investigators will have access to participant identifiable data. We will permit trial-related monitoring, audits and regulatory inspections and will provide direct access to source data and documents.

8.1.3 Data Security

The RCB systems are fully validated in accordance with industry and regulatory standards, and incorporate controlled access security. High volume servers are firewall protected and preventative system maintenance policies are in place to ensure no loss of service. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures.

8.1.4 Database Software

Data will be stored in MS SQL Server.

8.1.5 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, source document in accordance with ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained at the Data Centre for a minimum of 10 years.

8.1.6 Archiving

CRF data will be stored by the Robertson Centre for Biostatistics for 10 years after completion of the study.

9 STUDY MANAGEMENT

The trial management teams will be in place before recruitment begins.

9.1 Routine Management of Study

The study will be co-ordinated from the Glasgow Royal Infirmary, Glasgow by the PI. The study will be subject to review at any time by the West Glasgow Local Research Ethics Committee.

9.2 Trial Management Committee (TMC)

There will be no DSMC for this observational trial. Independent oversight will be provided by the study advisory group.

9.3 Data Safety Monitoring Committee (DSMC)

There will be no DSMC for this observational trial.

10 Study Monitoring and Auditing

Study monitoring visits will be conducted according to a study-specific monitoring plan devised by NHS Greater Glasgow and Clyde and subsequent monitoring reports will be reviewed by NHS Greater Glasgow and Clyde. The Sponsor, NHS Greater Glasgow and Clyde, audit a randomly selected 10% of studies conducted under the Research Governance Framework per annum, as well as those identified using a risk assessment tool as specifically requiring assessment. Investigators and site staff will notified in advance of any audit and/or monitoring visits.

11 Protocol Amendments

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the Chief Investigator and any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsor. The Sponsor will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the Chief Investigator and sponsor representative. Before the amended protocol can be implemented (or sent to other participating sites) favourable opinion/approval must be sought from the original reviewing REC and Greater Glasgow & Clyde Health Board Research and Development (R & D) office. The Chief Investigator will sign any amended versions of the protocol. All protocol versions and their amendments must be notified to the study team and to the data centre.

12 ETHICAL CONSIDERATIONS

12.1 Ethical Conduct of Study

Study will be carried on accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Seoul (2008) and Fortaleza (2013).

There are no special ethical considerations pertaining to this study. Favourable ethical opinion will be sought before patients are entered into this study. The Chief Investigator will update the ethics committee of any new information related to the study.

12.2 Informed Consent

The clinical team will assess study participant's ability to provide informed consent. Where possible we will obtain written informed consent from both study patient and informant.

Where a patient is unable to provide informed consent but clinical team are still happy for the person to participate in the study, informed consent will be sought from a suitable proxy. Choice of proxy will be guided by patient preference expressed at time of assessment or expressed pre-stroke.

The research nurse or trained member of the research team will explain the exact nature of the study in writing, provide patient and carer information sheets, and verbal information. Study participants will be informed that they are free to withdraw their consent from the study or study treatment at any time.

13 INSURANCE AND INDEMNITY

The study is sponsored by NHS Greater Glasgow and Clyde. The sponsors will be liable for negligent harm caused by the design of the trial. NHS Indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS). As the substantive employer of the CI, The University of Glasgow also has insurance with Newline. It will be confirmed prior to the study starting that insurance cover will be provided automatically under the current policy. The insurance cover will be subject to NHS indemnity being in place and Ethics Committee approval being obtained.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care.

As this is a clinician-led study there are no arrangements for no-fault compensation.

14 FUNDING

The study is funded by a Chief Scientist Office / Stroke Association Programme grant.

15 ANNUAL REPORTS

The funders mandate progress report and outputs to be submitted electronically via the Researchfish resource; these will be updated in real time and reviewed annually. Annual reports will be submitted to the ethics committee, regulatory authority and sponsor with the first submitted one year after the date that all trial related approvals are in place.

17 Dissemination of Findings

Study results will be submitted to an International Conference and will be submitted for publication in a peer review journal. No personal data will be used when publishing the results. A lay summary and other material as appropriate will be offered to those participants who wish to receive it. Participants will be asked at their last study visit if they are happy to be contacted and the preferred method for contact. These data will be held securely in the CRF in a password protected file that is separate from the main study archive.

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Appendix 3: Acquired Dementia 8 (AD8)

APPLE Study

Protocol Version 1.3

Version 3.0 (22 Jun 2017)

A: Baseline Informant Assessments

AD 8 Screening Interview

Page 1 of 10

Site Number _____ 01	Participant Number _____ 02	Initials _____ 03	Date of Visit D D M M Y Y Y Y 04
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Informant Initials _____ 05

A. AD 8 Screening Interview

Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	Yes, A change	No, No change	N/A, don't know
1. Problems with judgement (e.g. problems making decisions, bad financial decisions, problems with thinking)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2 <small>06</small>
2. Less interest in hobbies/activities	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2 <small>07</small>
3. Repeat the same things over and over (questions, stories, or statements)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2 <small>08</small>
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2 <small>09</small>
5. Forgets correct month or year	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2 <small>10</small>
6. Trouble handling complicated financial affairs (e.g., balancing cheque book, income taxes, paying bills)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2 <small>11</small>
7. Trouble remembering appointments	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2 <small>12</small>
8. Daily problems with thinking and/or memory	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2 <small>13</small>

Appendix 4: AMT10 and Mini-MoCA Assessment

APPLE Study

Protocol Version 1.5

Version 4.0 (26 Feb 2018)

Baseline Participant Assessments

AMT-plus

Page 1 of 14

Site Number	Participant Number	Initials	Date of Visit	
<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
Score 1 Point		Untestable - Reason (enter appropriate number from table on page 13)		Number of mistakes
1. Age	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
2. Time	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
3. Date	Day: Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2 Month: Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2 Year: Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
4. Place	Place: Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2 City: Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
5. Two person recognition	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
Give recall items at this point: face, velvet, church, daisy, red				N/A
6. Date of birth	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
7. World War 1	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
8. Prime Minister	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
9. Count 20-1	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	<input type="text"/>	
10. Recall (items)	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	<input type="text"/>	
11. Clock Draw	Face: Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2 Numbers: Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2 Hands: Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
12. News item	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	N/A	
13. Months backwards	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	<input type="text"/>	
14. One letter fluency	Yes <input type="checkbox"/> 1 No <input type="checkbox"/> 2	UN <input type="text"/> <input type="text"/> If other (9), specify: <input type="text"/>	Number of words <input type="text"/>	

1. Time taken to complete seconds
2. Verbal assistance required to complete Yes 1 No 2
3. Hands on assistance required to complete Yes 1 No 2

*Mini MoCA questions were 3, 10, 11 & 14. Scoring for Mini-Moca: question 3= 1 point for each part of date (day, month and year) recalled correctly (out of 3); question 10= 1 point for each word (face, velvet, church, daisy, red) recalled correctly (out of 5); question 11= 1 point for each part of clock (face, numbers, hands) drawn correctly (out of 3); question 14= 1 point if >10 words in 1 minute.

Appendix 5: Chapter 4, search syntax for systematic review

Search A

Pre-stroke depression focus search:

1. pre-stroke.mp.
2. prestroke.mp.
3. premorbid.mp.
4. 1 or 2 or 3
5. Mood Disorder Questionnaire/ or mood change/ or "Profile of Mood States"/ or mood/ or mood stabilizer/ or mood.mp. or mood disorder/ or mood disorder assessment/
6. depression/
7. 5 or 6
8. 4 and 7
9. limit 8 to human
10. (depressi\$ adj2 "before the stroke").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. (depressi\$ adj2 "history of").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

12. 1 or 2 or 3 or 10 or 11

13. 12 and 7

14. limit 13 to human

15. stroke/

16. 14 and 15

Search B

Post-stroke depression search:

1. exp Cerebrovascular Disorders/

2. stroke*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

3. poststroke*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

4. cerebrovascular*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

5. cerebral vascular.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

6. 2 or 3

7. 4 or 5

8. infarct*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

9. isch?emi*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

10. thrombo*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

11. emboli*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

12. apoplexy.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

13. 8 or 9 or 10 or 11 or 12

14. cerebral.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

15. intracerebral.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

16. intracranial.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

17. brain*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

18. cerebellar.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

19. vertebrobasilar.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

20. 14 or 15 or 16 or 17 or 18 or 19

21. h?emorrhage.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

22. bleed.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]

23. 21 or 22

24. 13 and 20

25. 20 and 23

26. 1 or 6 or 7 or 24 or 25

27. Depression/

28. Depressive Disorder/

29. 27 or 28

30. 26 and 29

31. limit 30 to human

Appendix 6: Chapter 4 Risk of bias assessment rationale

Prevalence:-

Specifically, studies were assessed based upon 1) whether the study had a particular focus upon assessment of pre-stroke depression, 2) if the studies cohort was recruited in an acceptable way, 3) if the study population's stroke diagnosis was consistent with WHO criteria, 4) risk of over/under estimation in reported pre-stroke depression rates, and 5) the generalisability of their study population:

- 1) A study was required to explicitly state intention to investigate pre-stroke depression (or at least pre-stroke psychological functioning) as a primary variable of interest (either to determine prevalence or association with a post-stroke outcome) to be considered to have a particular focus on pre-stroke depression. If a study assessed pre-stroke depression simply to control for it as a covariate, it was not deemed to have a particular focus on pre-stroke depression.
- 2) Recruitment was required to be based upon consecutive admissions to a given setting; i.e. a non-pre-selected stroke population. Studies that failed to do this would be scored as being high risk of bias.
- 3) Stroke diagnosis was considered to be consistent with WHO if explicitly stated, or if diagnosis was described in sufficient detail as to be likely to be consistent with WHO. If no information was given regarding how the stroke was defined, studies were classified as being of unclear risk of bias. If diagnosis was inconsistent with WHO, it was deemed to be at high risk of bias.
- 4) Risk of over/underestimation was based upon means of assessment and restriction placed within those assessments. For instance, if studies assessed pre-stroke depression using medical records, they were deemed to be at risk of underestimating pre-stroke depression since receiving a formal diagnosis of depression requires patients to seek help for their depression, which not

everyone will do. Similarly, self-report methods that asked patients if they had ever been diagnosed with depression suffer in this same way, but with added recall or social desirability influences that could further affect reported rates. Informant questionnaires were limited in that they require an informant to know about the patient's prior psychiatric history; and screening tools are liable to overestimate cases of depression. On this basis, assessment via a comprehensive clinical interview that established cases of depression based on reported symptoms meeting DSM criteria—rather than simply existent diagnosis, evidence of treatment for depression, or symptoms not well defined enough to establish DSM criteria (e.g. screening tool cut-offs)—was deemed to be the only method that minimised bias to an acceptable level and as such would be scored as low-ROB. All other assessment methods were scored as high-ROB. Studies in which the assessment method was unclear were scored as unclear ROB.

5) Since our exclusion criteria rejected studies with particularly poor population generalisability, generalisability assessments in the ROB review were predominantly based upon the exclusion of patients whose issues may affect reported pre-stroke depression rates. For example, pre-stroke dementia, pre-stroke disability, first ever strokes only, concurrent psychiatric disorders, previous alcohol or drug misuse were deemed as being high risk of bias; age restrictions or exclusion of TIA's were deemed unclear risk of bias due to reduced overall generalisability of population. Studies were also scored as having a high risk of bias in this category if there was uncertainty regarding the overall generalisability of their inclusion criteria.

Model assessment:-

Of the covariates controlled for, the most commonly cited variable associated with post-stroke depression across four systematic reviews was 'post-stroke functional impairment' or 'stroke severity'. [1-4] As post-stroke functional impairment and stroke severity are highly linked [5], we required all studies to control for one of these variables to achieve a positive ROB review in this category. The 'event-covariate ratio' category required studies to have 10 events (i.e. cases of PSD) per covariate controlled for in their model [6,7]. For

‘collinearity control’, studies were deemed to meet this criterion if they ran their multiple regression using stepwise measures or alternatively ran explicit collinearity tests. We also judged the quality of the statistical model based upon control for changes in care pathway. Altered care-pathway has been demonstrated to be a potential consequence of detection of pre-stroke depression in clinical practice. Specifically, reports suggest that patients with pre-stroke depression are more likely to be administered prophylactic (preventative) treatment for post-stroke depression, in addition to an increased likelihood to be referred for psychological consult [8,9]. We felt that both of these variables could impact any reported associations between pre-stroke depression and post-stroke depression, but were unlikely to be controlled for in studies (via records of post-stroke care accessed by each patient). As such, it was included as a secondary attribute for RoB assessment.

Sub group categorisation details

Assessment method classification:

Assessment methods were classified as follows: ‘self-report’ (any method that simply required a patient to inform as to a prior diagnosis of- or treatment for- depression, as part of a questionnaire or non-clinical interview), ‘medical records’ (hospital charts, admin records etc.), ‘clinical interview’ (both structured, semi-structured and unstructured in depth interviews conducted by a clinician; or alternatively, by a researcher using a tool such as the Structured Clinical Interview for Depression), ‘informant report’ (any assessment method in which *only* the informant was asked for pre-stroke depression information), ‘screening tool’ (validated tools for assessing depressive symptoms, such as the CESD). Where studies utilised more than one assessment method, we classified the assessment type via the method that we felt was most likely to have identified the highest number of pre-stroke depression cases reported in each study’s sample. Generally, Clinical Interviews took precedence over all other assessment types apart from screening tools. Based on findings from previous research [10], medical records took precedence over self-reports. A breakdown of the methods of assessment utilised in included studies can be seen in Table 3.

Risk of Bias (ROB) assessment rationale references

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3. Kutlubaev MA, Hackett ML. 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* 2014;**9**(8):1026-36 doi: 10.1111/ijss.12356 [published Online First: Epub Date]
4. Robinson RG, Jorge RE. Post-stroke depression: A review. *American Journal of Psychiatry* 2016;**173**(3):221-31
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8. Reid DL, Jia H, Cameon R, et al. Does prestroke depression impact poststroke depression and treatment? *AM J Geriatr Psychiatry* 2010;**18**:624-23

9. Slater K, McClure AJ, Mahon H, et al. Adherence to Canadian Best Practice Recommendations for Stroke Care: Assessment and Management of Poststroke Depression in an Ontario Rehabilitation Facility 2012. *Topics in Stroke Rehabilitation*; **19**(2):132-140

10. Wu C-S, Lai M-S, Gau SS-F, Wang S-C, Tsai H-J Concordance between Patient Self-Reports and Claims Data on Clinical Diagnoses, Medication Use, and Health System Utilization in Taiwan. *PLoS ONE* 2014; **9**(12): e112257.
doi:10.1371/journal.pone.0112257

Appendix 7: Chapter 4, prevalence GRADE table

Quality criteria	Rating (circle one for each criterion)	Footnotes (explain reasons for up- or downgrading)	Quality of the evidence (Circle one per outcome)
Outcome # 1: Pre-stroke depression prevalence			
Risk of bias	serious (-1)	All studies were graded as having a risk of bias in at least one category of the ROB assessment.	⊕⊕⊕⊕ High ⊕⊕⊕○ Moderate ⊕⊕○○ Low ⊕○○○ Very Low
Inconsistency	very serious (-2)	Very high I-squared and variability in reported rates.	
Indirectness	serious (-1)	Majority of studies did not have a specific interest in assessing pre-stroke depression.	
Imprecision	No	Confidence intervals are narrow.	
Publication Bias	Unlikely	No reason to base publication on basis of reported pre-stroke depression prevalence rate.	
Large effect	NA	NA	
Dose-response gradient	No	NA	
Plausible confounding would change the effect	No	NA	

Appendix 8: Chapter 4, included Studies that reported on the association between pre-stroke depression and post-stroke depression

Total studies that describe the association between pre-stroke depression and post-stroke depression	Studies that reported a <i>significant</i> ($p < 0.05$) association between pre-stroke depression and post-stroke depression	Studies that assessed pre-stroke depression/post-stroke depression association using multiple regression analysis	Studies that report a significant association between pre-stroke depression and post-stroke depression using multiple regression analysis
McCarthy et al., 2016; Schottke & Giabbiconi, 2015; De Ryck et al., 2013; White et al., 2014; Aben et al., 2006; Prisie et al., 2016; Tang et al., 2011; Zhang et al., 2010; Bara et al., 2016; Cairo et al., 2006; Gillen et al., 2001; Hackett et al., 2006; Jorgensen et al., 2016; Kim et al., 2014; Kootker et al., 2016; Liu et al., 2017; Ng et al., 1995; Paolucci et al., 2006; Pohjasvarra et al., 1998; Sienkiewicz-Jarosz et al., 2010; Singh et al., 2000; Tang et al., 2005; Tse et al., 2017; Verdelho et al., 2004	McCarthy et al., 2016; De Ryck et al., 2013; Prisie et al., 2016; Tang et al., 2011; Zhang et al., 2010; Caeiro et al., 2006; Gillen et al., 2001; Kim et al., 2014; Ng et al., 1995; Paolucci et al., 2006; Pohjasvarra et al., 1998; Verdelho et al., 2004	McCarthy et al., 2016; Schottke & Giabbiconi, 2015; De Ryck et al., 2013; White et al., 2014; Aben et al., 2006; Tang et al., 2011; Zhang et al., 2010; Bara et al., 2016; Cairo et al., 2006; Hackett et al., 2006; Jorgensen et al., 2016; Ng et al., 1995; Paolucci et al., 2006; Pohjasvarra et al., 1998; Verdelho et al., 2004	McCarthy et al., 2016; De Ryck et al., 2013; Tang et al., 2011; Zhang et al., 2010; Cairo et al., 2006; Hackett et al., 2006; Jorgensen et al., 2016; Ng et al., 1995; Paolucci et al., 2006; Pohjasvarra et al., 1998; Verdelho et al., 2004

Appendix 9: Chapter 4, table of Pre-stroke depression/post-stroke depression risk association study heterogeneity

Study	Pre-stroke depression assessment method	Post-stroke depression assessment method	Covariates controlled for
Aben et al. (2006)	SCID*	SCID	Sex; Somatic comorbidity; family history of depression
Barra et al. (2016)	Medical records	HADS [§]	Age; sex; mRS [§] ; previous stroke.
Caiero et al. (2006)	Semi-structured clinical interview	MADRS [^] (Cut-off 7)	Age; sex; aphasia.
De Ryck et al. (2013)	1)Self-report 2)Medical records/charts 3)Screening (CSD [§])	CSD and MADRS	BI [£] ; NIHSS [£] ; mRS; [¶] FIM; [¶] MMSE; [¶] SIS
Hackett et al. (2006)	Self-report	GHQ-28 ⁺	Sex; age; comorbidity; BI; premorbid dependency; loss of consciousness.
Jorgensen et al. (2016)	Medical records	Medical records	Age; sex; education; cohabitation status; diabetes.
Mcarthy et al. (2016)	Medical records and self-report	CESD [#]	Sex; race; marital status; education; NIHSS; mRS; age;
Ng et al. (1995)	Clinical Interview	Clinical interview (DSMIII ^B) and HDRS ^A	Age; sex; Lesion type; functional status.
Paolucci et al. (2006)	Self-report	BDI (>10) or "sad face" on VAMS	Sex; prev stroke; mRS; aphasia; BI.
Pohjasvarra et al. (1998)	Medical records	Neuropsychiatric inventory (DSMIII and ICD10 ^C)	Dependence; BI; Stroke severity scale.
Schottke et al. (2015)	SCID	SCID	Life-time anxiety disorders.
Tang et al. (2011)	Medical records and self-reports	SCID	Sex; lesion location; education; NIHSS; Social network; Life events.
Verdelho et al. (2004)	Medical Records and self-reports	CAMDEX [£] and MADRS	Sex; prev stroke; prev dementia; stroke characteristics; mRS; Orgozo score; post-stroke dementia.
White et al. (2014)	Medical records	HADS	Time; age; mRS; social support; Sex; activities; anxiety; baseline depression.
Zhang et al. (2010)	CIDI [!]	CIDI	Gender; marital status; Hypertension; mRS; HDRS.

Appendix 10: Chapter 4, pre-stroke depression/post-stroke depression risk association GRADE table

Quality criteria	Rating (circle one for each criterion)	Footnotes (explain reasons for up- or downgrading)	Quality of the evidence (Circle one per outcome)
Outcome #2: Risk association with post-stroke depression			
Risk of bias	serious (-1)	Most studies had potential sources of bias in primary ROB categories. All studies were at risk of bias based upon possible variations in care pathway.	⊕⊕⊕⊕ High ⊕⊕⊕○ Moderate ⊕⊕○○ Low ⊕○○○ Very Low
Inconsistency	No	Vast majority of studies suggest similar sized odds ratios.	
Indirectness	serious (-1)	Pre-stroke depression was assessed as a covariate in a number of regression models and hence was not a primary variable of interest.	
Imprecision	No	Confidence intervals are narrow.	
Publication Bias	very likely (-2)	Studies often do not provide odds ratios if not significant.	
Large effect	Large (+1)	>3 odds ratio	
Dose-response gradient	No	NA	
Plausible confounding would change the effect	No	Confounders such as care pathway could conceivably increase or decrease effect size.	

Appendix 11: Stroke Aphasic Depression Questionnaire (SADQ-H10)

APPLE Study

Protocol Version 1.3

Version 3.0 (22 Jun 2017)

B: Baseline Informant Assessments
Stroke Aphasic Depression Questionnaire (SADQ-H 10)
Page 4 of 10

Site Number _____01	Participant Number _____02	Initials _____03	Date of Visit D D M M Y Y Y Y 04
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Informant Initials _____05

Please indicate how many days of the last 7 the participant has shown the following behaviours:

	Every day this week	On 4-6 days this week	On 1-4 days this week	Not at all this week
1. Did he/she have weeping spells?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 06
2. Did he/she have restless disturbed nights?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 07
3. Did he/she avoid eye contact when you spoke to him/her?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 08
4. Did he/she burst into tears?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 09
5. Did he/she indicate suffering from aches and pains?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 10
6. Did he/she get angry?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 11
7. Did he/she refuse to participate in social activities?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 12
8. Did he/she sit without doing anything?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 13
9. Did he/she keep him/herself occupied during the day?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 14
10. Did he/she get restless and fidgety?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3 15

Produced by Robertson Centre for Biostatistics, University of Glasgow

Appendix 14: Chapter 6, associations between factors and death within 1 year

	<u>Unadjusted</u>		<u>Adjusted</u>	
	<u>OR (95% CI)</u>	<u>p-value</u>	<u>OR (95% CI)</u>	<u>p-value</u>
Age (by year)	1.08 (1.07,1.09)	<0.001	1.04 (1.02,1.06)	<0.001
Male	0.65 (0.55,0.77)	<0.001	0.79 (0.6,1.06)	0.111
Pre-stroke rankin		Trend:<0.001		Trend:<0.001
1 vs 0	2.23 (1.69,2.94)	<0.001	1.88 (1.29,2.74)	0.001
2 vs 0	2.82 (2.03,3.92)	<0.001	1.85 (1.2,2.85)	0.005
3 vs 0	5.48 (3.99,7.51)	<0.001	3.43 (2.24,5.25)	<0.001
4 or 5 vs 0	11.97 (8.4,17.04)	<0.001	6.84 (4.24,11.03)	<0.001
ICH	2.28 (1.79,2.89)	<0.001	3.99 (2.69,5.9)	<0.001
MEWS	1.32 (1.23,1.41)	<0.001	1.18 (1.07,1.31)	0.001
Glucose	1.07 (1.04,1.10)	<0.001	1.06 (1.02,1.11)	0.008
AF	2.08 (1.73,2.52)	<0.001	1.59 (1.2,2.12)	0.001
Charlson index	1.37 (1.32,1.43)	<0.001	1.17 (1.08,1.26)	<0.001

ICH= Intracerebral haemorrhage; MEWS= Modified Early Warning Score; AF= Atrial fibrillation

Appendix 15: Chapter 6, associations between factors and death within 7 days.

	<u>Unadjusted</u>		<u>Adjusted</u>	
	<u>OR (95%CI)</u>	<u>p-value</u>	<u>OR (95%CI)</u>	<u>p-value</u>
Age	1.04 (1.03,1.05)	<0.001	1.02 (1,1.04)	0.11
Male	0.77 (0.59,0.99)	0.045	1.01 (0.64,1.58)	0.98
Pre-stroke Rankin		Trend:<0.001		Trend:<0.001
1 vs 0	1.62 (1.04,2.50)	0.031	1.83 (0.97,3.44)	0.06
2 vs 0	1.79 (1.06,3.01)	0.029	2.24 (1.11,4.5)	0.024
3 vs 0	2.12 (1.30,3.46)	0.003	2.54 (1.3,4.96)	0.006
4 or 5 vs 0	5.58 (3.68,8.46)	<0.001	4.39 (2.32,8.28)	<0.001
ICH	5.03 (3.75,6.75)	<0.001	8.22 (5.14,13.15)	<0.001
MEWS	1.68 (1.53,1.85)	<0.001	1.6 (1.38,1.84)	<0.001
Glucose	1.09 (1.05,1.13)	<0.001	1.06 (1,1.12)	0.035
AF	1.48 (1.12,1.95)	0.006	1.16 (0.74,1.81)	0.518
Charlson index	1.16 (1.10,1.22)	<0.001	1.09 (0.97,1.21)	0.137

ICH= Intracerebral haemorrhage; MEWS= Modified Early Warning Score; AF= Atrial fibrillation

Appendix 16: Chapter 6, association between factors and Urinary Tract Infection.

	<u>Unadjusted</u>		<u>Adjusted</u>	
	<u>OR (95%CI)</u>	<u>p-value</u>	<u>OR (95%CI)</u>	<u>p-value</u>
Age	1.02 (1.01,1.04)	0.005	1.04 (1.02,1.07)	0.002
Male	0.58 (0.41,0.82)	0.002	0.6 (0.37,0.97)	0.036
Pre-stroke Rankin		Trend: 0.090		Trend: 0.231
1 vs 0	2.32 (1.44,3.72)	<0.001	2.18 (1.2,3.96)	0.01
2 vs 0	2.93 (1.72,4.99)	<0.001	3.42 (1.79,6.53)	<0.001
3 vs 0	1.79 (0.97,3.28)	0.062	1.47 (0.68,3.16)	0.323
4 or 5 vs 0	1.04 (0.48,2.26)	0.916	1.21 (0.49,2.96)	0.682
ICH	0.93 (0.56,1.54)	0.772	0.96 (0.46,2)	0.922
MEWS	0.89 (0.77,1.03)	0.109	0.86 (0.71,1.03)	0.097
Glucose	0.99 (0.93,1.05)	0.674	0.97 (0.89,1.06)	0.552
AF	1.57 (1.10,2.26)	0.014	1.48 (0.93,2.35)	0.097
Charlson index	1.02 (0.95,1.09)	0.683	0.77 (0.64,0.92)	0.004

ICH= Intracerebral haemorrhage; MEWS= Modified Early Warning Score; AF= Atrial fibrillation

Appendix 17: Chapter 6, association between factors and Pneumonia.

	<u>Unadjusted</u>		<u>Adjusted</u>	
	<u>OR (95%CI)</u>	<u>p-value</u>	<u>OR (95%CI)</u>	<u>p-value</u>
Age	1.04 (1.03,1.06)	<0.001	1.04 (1.02,1.07)	<0.001
Male	0.86 (0.67,1.11)	0.243	1.09 (0.75,1.6)	0.639
Pre-stroke Rankin		Trend: 0.001		Trend: 0.001
1 vs 0	1.56 (1.02,2.38)	0.04	1.32 (0.78,2.23)	0.307
2 vs 0	2.06 (1.27,3.33)	0.003	1.67 (0.94,2.98)	0.081
3 vs 0	2.74 (1.76,4.26)	<0.001	1.53 (0.86,2.75)	0.15
4 or 5 vs 0	4.12 (2.7,6.29)	<0.001	2.79 (1.62,4.82)	<0.001
ICH	1.09 (0.76,1.56)	0.642	1.24 (0.74,2.08)	0.416
MEWS	1.31 (1.20,1.43)	<0.001	1.18 (1.04,1.34)	0.012
Glucose	1.06 (1.02,1.10)	0.002	1.06 (1.01,1.11)	0.025
AF	1.61 (1.24,2.11)	<0.001	1.38 (0.96,1.99)	0.086
Charlson index	1.14 (1.09,1.20)	<0.001	0.96 (0.86,1.06)	0.425

ICH= Intracerebral haemorrhage; MEWS= Modified Early Warning Score; AF= Atrial fibrillation

Appendix 18: Chapter 6, association between factors and Length of Stay.

	<u>Unadjusted</u>		<u>Adjusted</u>	
	<u>Beta (95%CI)</u>	<u>p-value</u>	<u>Beta (95%CI)</u>	<u>p-value</u>
Age	0.26 (0.20,0.32)	<0.001	0.2 (0.09,0.31)	<0.001
Male	-3.28 (-4.85,- 1.71)	<0.001	-1.56 (- 3.72,0.59)	0.155
Pre- stroke Rankin		Trend: <0.001		
1 vs 0	6.01 (3.78,8.24)	<0.001	5.68 (2.71,8.65)	<0.001
2 vs 0	6.11 (3.32,8.9)	<0.001	4.39 (0.81,7.96)	0.016
3 vs 0	9.28 (6.51,12.05)	<0.001	6.38 (2.77,10)	0.001
4 or 5 vs 0	3.58 (0.68,6.49)	0.016	1.06 (- 2.87,4.98)	0.597
ICH	1.52 (- 0.83,3.87)	0.204	2.79 (- 0.4,5.97)	0.086
MEWS	0.01 (- 0.62,0.64)	0.971	-0.15 (- 0.96,0.65)	0.707
Glucose	0.19 (- 0.10,0.48)	0.192	0.18 (- 0.17,0.52)	0.313
AF	5.53 (3.77,7.30)	<0.001	4.11 (1.83,6.4)	<0.001
Charlson index	0.85 (0.51,1.19)	<0.001	-0.38 (- 0.98,0.22)	0.219

ICH= Intracerebral haemorrhage; MEWS= Modified Early Warning Score; AF= Atrial fibrillation

Appendix 19: Chapter 6, association between factors and discharge destination ('Home' vs any one of 'Sheltered housing', 'Rehabilitation Centre' or 'Care home').

	<u>Unadjusted</u>		<u>Adjusted</u>	
	<u>OR (95%CI)</u>	<u>p-value</u>	<u>OR (95%CI)</u>	<u>p-value</u>
Age	1.04 (1.03,1.05)	<0.001	1.03 (1.02,1.05)	<0.001
Male	0.59 (0.49,0.70)	<0.001	0.64 (0.49,0.83)	0.001
Pre-stroke Rankin		Trend: <0.001		Trend: <0.001
1 vs 0	1.81 (1.41,2.33)	<0.001	2 (1.42,2.83)	<0.001
2 vs 0	2.17 (1.57,3)	<0.001	2.25 (1.47,3.45)	<0.001
3 vs 0	3.13 (2.15,4.57)	<0.001	2.62 (1.61,4.28)	<0.001
4 or 5 vs 0	3.61 (2.28,5.73)	<0.001	2.24 (1.2,4.19)	0.011
ICH	2.73 (2.10,3.56)	<0.001	3.7 (2.47,5.54)	<0.001
MEWS	1.24 (1.16,1.34)	<0.001	1.17 (1.06,1.29)	0.002
Glucose	1.08 (1.04,1.11)	<0.001	1.06 (1.01,1.11)	0.011
AF	1.95 (1.60,2.38)	<0.001	1.69 (1.28,2.24)	<0.001
Charlson index	1.16 (1.12,1.21)	<0.001	0.98 (0.91,1.06)	0.614

ICH= Intracerebral haemorrhage; MEWS= Modified Early Warning Score; AF= Atrial fibrillation

Appendix 20: Frailty Index

Frailty Index		
Depression	Haemoglobin (low)	Liver disease
Anxiety	Care-home resident	Peptic ulcer
Polypharmacy	Carers	Arthritis
Hypertension	Hearing aid	Impaired external ADL
Atrial Fibrillation	Sensory impairment (e.g.	Impaired ADL
Previous cerebrovascular disease	blind/deaf)	Mobility aid
Diabetes	Continence bladder	Assistance walking
Vascular disease	Continence bowel	Calcium
Hyperlipidaemia	Falls	Albumin (low)
Heart failure	Fracture	High glucose
Previous Myocardial infarction	Chronic Obstructive Pulmonary Disease	Renal failure
	Cancer	

Appendix 21: Frailty Phenotype self-report assessment

APPLE Study

Protocol Version 1.3

Version 3.0 (22 Jun 2017)

Baseline Participant Assessments
Fried Frailty Phenotyping: Pre-Stroke Function
Page 11 of 14

Site Number <input type="text"/>	Participant Number <input type="text"/>	Initials <input type="text"/>	Date of Visit <input type="text"/>
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PRE-STROKE FUNCTION

1. Have you lost more than 4 kg of weight (half stone)? (does not include intentional weight loss from dieting)	No <input type="checkbox"/> 0	Yes <input type="checkbox"/> 1
2. Have you any difficulties walking 400 meters (quarter mile)?	No or some difficulty <input type="checkbox"/> 0	A lot of difficulty / unable <input type="checkbox"/> 1
3. How often in the last week did you feel that everything was an effort or that you could not get going?	Twice or less <input type="checkbox"/> 0	Three or more times <input type="checkbox"/> 1
4. Have you had difficulty climbing up a flight of stairs?	No or some difficulty <input type="checkbox"/> 0	A lot of difficulty / unable <input type="checkbox"/> 1
5. What is your level of physical activity?	Regular activity (at least 4 hours) <input type="checkbox"/> 0	None or mainly sedentary <input type="checkbox"/> 1

A self-reported screening tool for detecting community-dwelling older persons with frailty syndrome in the absence of mobility disability: the FiND questionnaire

Cesari M, Demougeot L, Boccalon H, et al. A self-reported screening tool for detecting community-dwelling older persons with frailty syndrome in the absence of mobility disability: the FiND questionnaire. *PLoS One* 2014;9:e101745.

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