Anxiety After Stroke: Prevalence, Intervention Effectiveness, and Illness Representations

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The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Two systematic reviews that formed part of the work carried out in this thesis have been published. Carla Alexia Campbell Burton co-ordinated and led these reviews, developed the protocol and analysis plans, conducted data extraction and analysis and wrote and edited all drafts Review co-authors contributed to the design and conduct of the review and commented on various drafts that were circulated..

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Abstract

Stroke is a life changing event that can result in significant negative consequences. As such psychological disturbances may arise. In the general population anxiety is the most prevalent mental health condition, yet it remains under-researched and under-recognised within stroke survivors. Anxiety, is associated with decreased quality of life, increased healthcare utilisation, and increased severity of depression. The aims of the programme of research organised in this thesis were to establish a quantitative estimate of the prevalence of anxiety after stroke, to determine if there were any interventions that were effective in treating it and to uncover psychological factors that may have attributed to the manifestation of anxiety after stroke.

Three studies were conducted. The first was a systematic review and meta-analysis of observational studies that assessed the prevalence of anxiety after stroke. The second study was a Cochrane systematic review of randomised control trials to examine if any interventions were effective in treating anxiety after stroke. The third study was a longitudinal cohort study that used the common-sense model of illness representations (Leventhal, Meyer and Nerenz 1980) to uncover the illness beliefs held by stroke survivors, and to evaluate whether these beliefs were associated with anxiety after stroke.

Approximately 20% of stroke survivors were found to have an anxiety disorder, and 25% experienced significant levels of anxiety symptoms. Currently, there is insufficient evidence from randomised control trials to guide treatment of anxiety after stroke. Illness representations were relatively stable over time. Only higher illness identity (e.g. attributing a higher symptom burden to stroke), and having a more emotional response to ones stroke were associated with anxiety in stroke survivors.

Several limitations in all three studies may restrict the generalisability and validity of the findings and there are many questions that remain unanswered. However this work has contributed substantially to the investigation into the phenomenon of anxiety after stroke and can inform clinical guideline development, post-stroke psychological service provision and future intervention studies.

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Abbreviations

6-CIT	Six Item Cognitive Impairment Test
ANCOVA	Analysis of Covariance
BI	Barthel Index
CBT	Cognitive Behavioural Therapy
CSM	Common Sense Model of illness representations
CT	Computer Tomography
DA	Discriminant Analysis
DSM	Diagnostic and Statistical Manual of Mental Disorders
F.A.S.T.	Face Arms Speech Test
GAD	Generalised anxiety disorder
HADS	Hospital Anxiety and Depression Scale
IAPT	Improving Access to Psychological Therapies
ICD	International Classification of Diseases
IPQ	Illness Perception Questionnaire
IPQ-R	Illness Perception Questionnaire Revised
MANOVA	Multivariate Analysis of Variance
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NHS	National Health Service

NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
OCD	Obsessive compulsive disorder
PTSD	Post-traumatic stress disorder
RCT	Randomised Control Trial
SEM	Structural Equation Modelling
TIA	Transient ischaemic attack
UK	United Kingdom
WHO	World Health Organization

Preface

This thesis is organised into four main sections: introductory review chapters regarding stroke, anxiety, and the common sense model of illness representations; a systematic review of the prevalence of anxiety after stroke; a systematic review of interventions to treat anxiety after stroke; and a primary clinical longitudinal cohort study investigating illness representations held by stroke survivors and their association with anxiety.

The first three chapters (Chapters 1-3) serve as the background information for all three studies that were carried out. The systematic reviews are described in their entirety in two stand alone chapters (Chapters 4 & 5). The remainder of this thesis focuses primarily on the work carried out for the empirical longitudinal cohort study. A general methods chapter (Chapter 6) has been included which provides an outline of the research process and an analysis plan. In depth descriptions of the more complex analytical techniques employed in the empirical study have intentionally been placed adjacent to the results for readability purposes (Chapter 7 & 8). The final chapter (Chapter 9) integrates findings from all three studies, and provides a focused discussion on the strengths, limitations and implications of the empirical study, and assesses the implications of the entire body of work.

1 Chapter One: Overview of stroke

1.1 Introduction

Stroke is a major public health concern (Mackay and Mensah 2004), and its occurrence can have devastating and long lasting impact on the lives of the individual affected, and those closest to them. Until fairly recently, the societal perspective on stroke was generally fatalistic and dismissive, and the condition was simply regarded by many as an unfortunate consequence of ageing. Since then there have been substantial changes in health policy which have resulted in significant improvements in the way stroke care is organised and delivered (National Audit Office 2010). This has led to decreased mortality and improvement in stroke associated outcomes. The National Stroke Strategy, (Department of Health 2007) published in 2007, was heralded as a "national ambition for stroke" and proposed a series of high quality benchmarks that outlined actions and progress measures for the next ten years. This has brought about initiatives like the Stroke –Act F.A.S.T campaign, a public awareness campaign, which explains the key symptoms of stroke and emphasises that it is a medical emergency requiring immediate attention whereby the ambulance should be called. Ambulance services have changed the way in which they respond to individuals showing signs of a possible stroke, paramedics are better trained in recognising the signs of stroke and enhanced protocols for triaging individuals with suspected stroke have been established. The National Institute for Health and Clinical Excellence (NICE) have developed guidelines advocating that all patients suspected of stroke should be admitted directly to stroke units as there is clear evidence of benefit in doing so (National Institute for Health and Clinical Excellence 2010), and more stroke patients are accessing this service than ever before (Royal College of Physicians 2012). Additionally, significant resources have gone into increasing the proportion of acute stroke patients receiving neuro-imaging. This has led to an increase in the proportion of stroke patients receiving thrombolysis (a method of breaking down clots which if administered within 3-4 hours post-stroke can arrest or significantly reduce stroke associated complications) from 1% in 2008 to 8% in 2011 (Royal College of Physicians 2012).

The improvements highlighted above are but a few that have contributed towards saving lives and reducing levels of stroke-associated disability. Unfortunately, longer-term

post hospital discharge services and support have not matched the progress seen in acute services. The full impact of the stroke is often not realised until after the individual leaves the hospital, and endeavours to renegotiate their lives (Stroke Improvement programme 2010). A lack of health information and knowledge of available resources, combined with an inability to return to pre-stroke state and limited integration between health, social and community services leave many stroke survivors feeling fearful, abandoned and distressed. These issues can contribute to the manifestation of various psychological problems amongst stroke survivors. The recognition that mental health distress can have an impact on physical recovery and quality of life has lead to substantial investigation into post-stroke depression and emotionalism perhaps because the manner in which they manifest is rather salient. Anxiety on the other hand, which is the most common mental health disorder in the general population (Kessler *et al.* 2009) has received relatively little attention and has remained under-recognised within the stroke population, even though its impact may be just as significant.

The overall goal of this thesis is to investigate the phenomenon of anxiety after stroke. The purpose of this first chapter is to provide background information about stroke, its associated complications, and what it means to live with it, hence highlighting the various factors that may contribute to psychological distress, and anxiety in particular after stroke.

1.2 What is a stroke?

Stroke is defined by the World Health Organization as a rapidly developing clinical syndrome characterised by an acute loss of focal (or global) brain function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin (Hatano 1976). The somewhat arbitrary cut-off of 24 hours distinguishes stroke from a transient ischaemic attack (TIA), where symptoms and signs last for less than 24 hours.

The physiological mechanisms underlying TIA and stroke are similar, however the aims of clinical investigation differ in approach. With TIAs the focus is primarily on rapid identification and treatment of the underlying causes in order to prevent a recurrent or possibly more severe event. In stroke the initial emphasis of investigation is on targeting treatment to minimise subsequent deficit (Pendlebury, Giles and Rothwell 2009). However,

in practice the distinction between stroke and TIA can only be made retrospectively and may be of little importance.

1.3 Impact of stroke

Globally, it is estimated that 16 million people will suffer from a first-ever stroke each year (Strong, Mathers and Bonita 2007). Stroke is the second leading cause of death behind coronary heart disease, and is the leading cause of adult disability (World Health Organization 2011; Mackay and Mensah 2004).

In England and Wales, approximately 110,000 strokes and a further 20,000 TIAs occur each year (National Audit Office 2005). There are over 900,000 people living with stroke, and about a third have moderate to severe disability (Pendlebury, Giles and Rothwell 2009). While generally regarded as a disease associated with ageing, approximately 25% of strokes occur in persons under the age of 65 years. Stroke is also the second leading cause of death, accounting for 7% of all male deaths and 10% of all female deaths (Office for National Statistics 2011). Despite an ageing population, stroke incidence has fallen steadily over the last 10 years, while the prevalence of stroke (the proportion who survive) has increased (Rothwell *et al.* 2004; Lee, Shafe and Cowie 2011). Additionally, mortality rates have declined significantly, with the proportion who die within one month of having a stroke decreasing from 20% -30% in the 1990s to 12% in 2008 (Wolfe 2000; Lee, Shafe and Cowie 2011).

The annual direct healthcare costs associated with stroke are estimated to be £2.8 billion in the UK, with an average length of stay in hospital of around 28 days (Saka, McGuire and Wolfe 2009). Comparatively, coronary heart disease which is the leading cause of morbidity and mortality in the UK costs £1.9 billion per year, and has an average length of stay of seven days (National Audit Office 2005). Informal care and time spent by carers of disabled stroke patients, along with potential loss of lifetime earnings or premature death is said to cost another £4 billion each year (Saka, McGuire and Wolfe 2009).

1.4 Stroke subtypes and pathophysiology

Strokes are either ischaemic or haemorrhagic. Because the management of these subtypes are so different, their clinical distinction is one of the most important and urgent

steps in stroke management. Ischaemic stroke occurs when the blood (and glucose and oxygen) supply to part of the brain is cut off, leading to dysfunction or death of the brain tissue in that area (Hankey 2002). Ischaemic stroke arise due to either *thrombosis* (a condition where a blood clot forms inside an artery in the brain, blocking blood flow), or *embolism* (when a clot that that formed elsewhere in the body, dislodges and becomes trapped in arteries closer to the brain). TIAs are classified as ischaemic stroke.

There are two subtypes of haemorrhagic stroke. The first, intracerebral haemorrhage, occurs when a defective artery within the brain ruptures and fills the surrounding brain tissues which leads to brain structures being compressed. A subarachnoid haemorrhage differs from an intracerebral haemorrhage in that the blood from a ruptured artery fills the space surrounding the brain (the subarachnoid space) rather than inside of it (Hankey 2002).

Approximately 85% of all first-ever strokes are ischaemic; 10% are caused by primary intracerebral haemorrhage, and 5% are subarachnoid haemorrhage (Rothwell *et al.* 2004). Haemorrhagic strokes are generally more severe and cause higher levels of mortality (Andersen *et al.* 2009).

Various systems have been developed to classify strokes. The Oxfordshire Stroke Classification, also known as the Bamford classification is one of the most widely used (Bamford *et al.* 1991). It is a robust system that is based on clinical signs and is useful for understanding the likely underlying pathology, which can inform prognosis, and treatment options. The four categories are: Lacunar infarct which is characterised by motor or sensory deficits only; Partial Anterior Cerebral Infarct (PACI) which is characterised by two of the following- unilateral or sensory loss or the face, arm, and leg, higher cortical dysfunction (e.g. dysphagia or visuospatial disorders) and hemianopia (visual field loss); Total Anterior Cerebral Infarct (TACI) which is defined by unilateral weakness and/or sensory deficit of the face arms or legs, hemianopia, and higher cerebral dysfunction; and Posterior Circulation Infarct (POCI) whose main features include either hemianopia, cerebellar dysfunction, or loss of consciousness.

1.5 Risk factors for stroke

Risk factors for stroke can be broadly classified as modifiable and non-modifiable. A large multi-national study found that a history of hypertension, tobacco smoking, high waist-to-hip ratio, high fat diet, physical inactivity, psycho-social stress, depression, high cholesterol, type 2 diabetes, and cardiac conditions (e.g. atrial fibrillation) explained 90% of stroke-associated risk (O'Donnell *et al.* 2010). TIA has been proposed as a risk for subsequent strokes, however a meta-analysis found that stroke re-occurrence after TIA ranged only from 1-12% (Giles and Rothwell 2007).

Advanced age is the strongest non-modifiable risk factor for ischaemic stroke and primary intracerebral haemorrhage, but is less important for subarachnoid haemorrhage. At age 75-84 years stroke incidence is approximately 25 times higher than at age 45-54 years (Rothwell *et al.* 2005). Ischaemic stroke is slightly more common in men than women. This gender difference is less marked for stroke than other cardiovascular diseases, such as coronary heart disease and peripheral arterial disease. In the UK rates of subarachnoid haemorrhage are slightly higher in women than in men (Rothwell *et al.* 2005). Racial and social differences have also been observed. For example, stroke incidence in the UK South Asian, Caribbean, and African populations have been found to be higher than those in the White-British population, perhaps due to higher prevalence of certain risk factors such as hypertension and diabetes in these groups (Pendlebury, Giles and Rothwell 2009). Additionally, the role of genetics has been investigated for its possible influence on stroke risk. There is some evidence to suggest that genetics and having a family history of stroke are associated with early age of stroke onset (Schulz, Flossmann and Rothwell 2004). Even though the contribution of genetic factors to stroke have not been conclusively established, they remain an area of research interest (Pendlebury, Giles and Rothwell 2009).

1.6 Complications of Stroke

Many stroke survivors experience close to a complete recovery, however for others the effects of the stroke can be catastrophic and result in having to live with some form of residual disability or impairment. The following section highlights some of the common longer term consequences of stroke that individuals have to manage.

1.6.1 Physical limitations

Physical impairment, problems in body function or structure including substantial deviation or loss (World Health Organization 2002), are the hallmark of stroke deficits. Weakness in the arms or legs is one of the most commonly occurring consequences of stroke. Approximately 80% of stroke survivors experience some problems with movement (Wolfe 2000). Unilateral paralysis (e.g. hemiparesis, which consists of paralysis on one side of the body) is common (Wade and Hewer 1987; Sommerfeld *et al.* 2004). As a result of the muscle weakness, spasticity may develop which may lead to pain or stiff muscles and joints. Loss of sensation on the affected side can give rise to problems with balance which are also common after stroke (Tyson *et al.* 2006). When balance is affected an individual may feel dizzy or unsteady which could result in falls or loss of confidence when walking or moving around. These physical problems can negatively impact on ones ability to perform routine daily and quality of life (Clarke and Black 2005).

1.6.2 Cognitive Impairment

Approximately one third of stroke survivors experience some form of generalised cognitive impairment (Patel *et al.* 2003; Pohjasvaara *et al.* 1997). Cognitive changes after stroke may manifest themselves as a general slowing down in information processing, or in changes in specific domains such as attention, memory visuospatial attention or planning and organising language (Cicerone *et al.* 2000; Cicerone *et al.* 2005). Some individuals may experience problems with reasoning or depending on the nature of the stroke lesion have limited awareness or lack of insight into their difficulties (Jehkonen, Laihosalo and Kettunen 2006). As many stroke survivors are older, it should be recognised that the cognitive impairment observed may have existed prior to stroke (Henon *et al.* 1997).

1.6.3 Communication problems

Communication problems are one of the most common consequences of stroke. Approximately one third of survivors have some difficulty with speaking or understanding (Wade *et al.* 1986; Pedersen *et al.* 1995). On initial assessment, Global aphasia (impairment in comprehension and production of speech), Broca's aphasia (inability to produce speech) and Wernicke's aphasia (inability to comprehend speech) were the most frequently

occurring forms of language deficits after stroke (Pedersen, Vinter and Olsen 2004). Dysarthia is a motor speech impairment that varies in severity and affects clarity of speech, voice quality and volume, and overall intelligibility. Roughly 20%-30% of patients experience it after stroke, and it may co-exist with aphasia (Scottish Intercollegiate Guidelines Network 2010). Dyspraxia, another type of communication problem occurs when the individual cannot move muscles in the correct order and sequence to make the sounds needed for clear speech (Lofgren *et al.* 1998).

1.6.4 Interpersonal and social impact

Feeling a loss of a purposeful role in life is a disheartening result of stroke. A review on the longer term consequences of stroke found that approximately 50% of stroke patients say they have no meaningful daytime activity, and one-third of younger survivors feel intellectually unfulfilled (Murray, Young and Forster 2007). Engaging in social activities can become quite challenging due to the physical consequences of stroke and many stroke survivors lack the ability to participate in routine community activities such as shopping or attending clubs (Barton 2007). Additionally the vast majority of working age stroke survivors do not return to work (Gabriele and Renate 2009). Some lose their ability to drive, which for many people is an important marker of independence. For older individuals, a stroke may be viewed as shattering planned hopes and aspirations of retirement life (Lobeck, Thompson and Shankland 2005). Sexual dysfunction after stroke is also common, and affects close to half of all survivors. Sexual dysfunction is linked with depression, older age, greater physical impairment and an unwillingness to discuss and participate in sexual activities, and while fear is also thought to be a contributing factor, this has yet to be confirmed (Murray, Young and Forster 2007).

1.6.5 Psychological problems

Aside from anxiety, which will be discussed extensively in chapter two, there are a range of psychological problems that can arise after stroke. Depression, which has been most extensively investigated, occurs in approximately one third of stroke patients (Hackett *et al.* 2005). While spontaneous recovery may occur, depressive symptoms may persist well beyond the first year after stroke for a substantial proportion of individuals. Depression

after stroke is associated with an increased risk of death and poor functional outcome (Hankey 2002).

Apathy, is another mental health problem that may arise after stroke (Yamagata, Yamaguchi and Kobayashi 2004) In some cases apathy is a symptom of depression but it may also occur on its own (Hama *et al.* 2011), yet unlike depression which is distressing to stroke survivors, apathy is more of a concern for caregivers.

About one quarter of stroke patients experience difficulty controlling the way in which they express emotion in the year following a stroke (Hackett *et al.* 2010). This condition is known as emotionalism, and manifests itself as abrupt crying or in some cases uncontrollable laughter that may be triggered by a thought or being asked a question with emotional overtones. While the outbursts may be of short duration, they can cause considerable distress to patients and their carers, and may be a significant obstacle to rehabilitation and social integration. Additionally uncontrollable anger or aggression which has been found to be related to emotionalism is reported in up to a third of patients, and is more prevalent in patients with severe motor dysfunction or dysarthria (Kim *et al.* 2002).

Anosognosia is a condition in which a person seems unaware of the existence of his or her disability (American Psychiatric Association 2000). Unlike denial, which is a defence mechanism, anosognosia occurs due to brain damage localised to specific areas (Robinson 2004). It is associated with negative prognosis, and compromises the course of recovery and rehabilitation. A recent review estimated the occurrence of post-stroke anosognosia to be between 10%-17%, with recovery most likely within the first three months (Orfei *et al.* 2007).

Loss of self-esteem may also be a concern. Self-esteem is the extent to which an individual has a positive or negative view of themselves (Brumfitt and Sheeran 1999). One study found that close to 20% of stroke survivors reported reduced levels of self-esteem, which in turn was found to be associated with higher levels of anxiety and depression (Vickery 2006). The stability of self-esteem has also been found to be associated with low mood. Individuals with high but unstable self-esteem, or those with low but stable self-esteem, were both more likely to suffer with symptoms of depression (Vickery *et al.* 2009).

Stroke survivors may also display a substantial amount of anger which can manifest as intense displeasure, offence or exasperation. Some of the physical limitations of stroke, the inability to participate in conversations or social settings, or being made to feel helpless have been noted as factors that trigger anger (Kim *et al.* 2002). Anger is associated with an increased risk of hypertension and depression, and may lead to taking up health harming behaviours such as smoking.

1.6.6 Other difficulties

An exhaustive list of all problems that may arise as result of stroke is not possible. However several other important symptoms that have been observed include fatigue (Glader, Stegmayr and Asplund 2002), financial strain (Murray, Young and Forster 2007), carer distress, and chronic pain (Murray, Young and Forster 2007).

1.7 Experience and satisfaction with services

Upon having a stroke, individuals have contact with several services along the stroke care pathway including: ambulance; accident and emergency; stroke unit; inpatient rehabilitation; early supported discharge; and specialist community stroke teams or generic community healthcare teams. Additionally, they may receive support from voluntary sector organisations such as Stroke Clubs, the Stroke Association and Different Strokes. A survey of over 1700 stroke survivors found that over 80% were satisfied with the follow-up care they received from their GP, but were much less positive about other aspects of care they had received since being discharged from hospital (Healthcare Commission 2006). In hospital, care was generally viewed more favourably than the care available post-discharge. Additionally, some indicated they had trouble dealing with some of the emotional and psychological consequences they were experiencing but nearly half of these individuals said they had not received enough support in this area (Healthcare Commission 2006). Subsequent national audits have also reported low ratings for psychological services available post stroke (National Audit Office 2010).

1.8 Living with stroke

The previous sections provided an overview of the possible consequences of stroke, and experiences with services, but what does it mean to actually have to live with this long-

term condition? The National Stroke Strategy for England and Wales highlighted the need for changes to the organisation and delivery of long-term stroke care once patients have been discharged from hospital. Various pilot projects are underway with the aim of identifying best practices that can be delivered across the entire country (Stroke Improvement programme 2010). Quality marker 12 in the National stroke strategy advocates for a seamless transfer of care from hospital to home (Department of Health 2007). This would entail a clear and workable discharge plan that has fully involved the individual (and their family when applicable) and which responds to the individual's circumstances and needs. Quality marker 13 in the strategy proposes that a range of services should be in place and easily accessible to support the long-term needs of individuals (and carers). It explicitly indicates that psychological, emotional, and adjustment supports should be available for individuals living in the community and those in care homes as well.

While such benchmarks are a move in the right direction, the current reality is not reflective of the advocated standards. There is significant disparity in resources and care available depending on where in the country one resides leaving the current situation to be described as a "postcode lottery"(McKevitt *et al.* 2011). Many stroke survivors indicate they face huge challenges once discharged from hospital and many are struggling to recover and adjust.. A recent survey of over 2200 stroke survivors indicated that they need support to stay at home, but felt very isolated once discharged from hospital. Others had to move to different parts of the country to access services that were not available where they lived, and 45%- 70% reported that they did not have a clear care plan in place prior to being discharged (McKevitt *et al.* 2011).

These examples highlight some of the many challenges of adjustment that stroke survivors face. They are also contributory factors that may influence ones beliefs (illness representations) about their stroke prognosis. The concept of illness representations (Leventhal, Meyer and Nerenz 1980) and their possible of association with anxiety after stroke is introduced in chapter three. Whether the transition to life after stroke is successful is contingent on a variety of factors. In a review of biographical accounts, the emergency treatment services, the hospital care environment including staff, community service, and social supports were key elements that determined whether stroke survivors

could be resilient and adapt to their situation, or whether they would spiral into a state of psychological distress (Lincoln *et al.* 2012).

1.9 Summary

Having a stroke is a life changing event with complications that may lead to a range of problems. This chapter provided an overview of stroke, and the complications that may manifest as a result. The aim was to set the scene for understanding the issues faced by stroke survivors which can give rise to psychological distress, and anxiety in particular, and which may also influence the development of illness beliefs. The concepts of anxiety and illness representations are explored in detail in the following two chapters.

2 Chapter Two: Literature Review- Anxiety

"Anxiety kills relatively few people, but many more would welcome death as an alternative to the paralysis and suffering resulting from anxiety in its severe forms. – Barlow 2002 p.18 (Barlow 2002)

2.1 Introduction

Changes in approach to stroke management from a fatalistic perspective with little possibility of improvement or recovery to its recognition as a long-term condition with rehabilitation potential, has generated interest in mental health outcomes that may occur after stroke. Depression and emotionalism after stroke have been observed and researched extensively (Ferro, Caeiro and Santos 2009). Anxiety disorders or clinically significant levels of anxiety symptoms in the stroke population have received substantially less attention, even though they are the most commonly occurring mental health problem in the general population (Kessler *et al.* 2009).

This chapter will provide an overview of anxiety disorders and symptom screening, explain why examining both is important, and describe how anxiety will be conceptualised within the context of this thesis. Diagnostic challenges, a review of the epidemiology, risk factors, the impact and treatment approach and options for anxiety are explored. Because the literature on anxiety after stroke is scant, references from depression after stroke or populations with other chronic long-term conditions are drawn on throughout. This chapter also serves as the background for chapters four and five where systematic reviews of the prevalence of anxiety after stroke, and interventions used to treat anxiety post-stroke are discussed in detail.

2.2 Anxiety after stroke- overview of the disorder and symptoms

Stroke can lead to the manifestation of various psychological and emotional disturbances (Hackett *et al.* 2005; House *et al.* 1989), however anxiety post-stroke has received comparatively less attention than more prominent psychological conditions such as depression.

Anxiety is a universally experienced emotion which exists on a continuum from normal to pathological. There is no universally agreed upon definition for this state but a

commonly accepted account describes anxiety as a diffuse state *" characterised by unpleasant affective experiences marked by a significant degree of apprehension about the potential appearance of future aversive or harmful events*" (DiTomasso and Gosch 2002 p.12) . Fear is a prominent feature of anxiety, and the two terms are often used interchangeably in the common vernacular. However from a phenomenological perspective fear is deemed to have a clear object and is usually elicited by an imminent threat. In the case of stroke survivors, this has been shown to manifest itself in several ways such as fear of falling (Watanabe 2005), stroke recurrence (Townend *et al.* 2006), or returning to work (Gilworth, Phil and Cert 2009). Anxiety on the other hand tends to be more generalised, is not necessarily linked to a specific cue, and represents the expectation of negative events or outcomes at some time in the future (Feinstein 2010), which goes beyond a simple fear of a situation or object.

Anxiety disorders are a collection of mental disorders characterised by a combination of key features that include excessive fear, worry, avoidance, or compulsive rituals, and are associated with impaired functioning or significant distress (Canadian Psychiatric Association 2006). Certain criteria can help identify when anxiety becomes a problem and warrants a diagnosis as a disorder (Table 2-1). While helpful, these criteria are based primarily on identifying anxiety in otherwise healthy individuals. Specific challenges associated with assessing anxiety after stroke will be discussed in section 2.3.

Table 2-1 Criteria to determine when anxiety becomes a disorder

Anxiety becomes a problem, and a disorder should be considered when:

- It is of greater intensity and (or) duration than usually expected, given the circumstances of its onset (consider context of family, societal, and cultural behaviour and expectations)
- It leads to impairment or disability in occupational, social, or interpersonal functioning
- Daily activities are disrupted by the avoidance of certain situations or objects in an attempt to diminish the anxiety
- It includes clinically significant, unexplained physical symptoms and (or) obsessions, compulsions, and intrusive recollections or memories of trauma

Taken from the Canadian Anxiety Management Clinical Practice Guidelines(Canadian Psychiatric Association 2006)

A broad spectrum of syndromes is included under the anxiety disorder umbrella. Manifested symptoms may be physical (e.g. heart palpitations, shortness of breath), cognitive (e.g. feeling of losing control), or behavioural (e.g. avoidance of certain stimuli) (Gelder, Harrison and Cowen 2006). The publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association 1994) saw the acceptance of 12 distinct anxiety disorders in the formal nomenclature. They are: Panic (with or without agoraphobia), Agoraphobia without history of panic disorder, Generalised anxiety disorder (GAD), Social phobia, Specific phobia, Obsessive compulsive disorder (OCD), Post-traumatic stress disorder (PTSD), Acute stress disorder, Anxiety disorder due to a general medical condition, substance-induced anxiety disorder, and Anxiety disorder not otherwise specified. A thirteenth category, mixed anxiety-depressive disorder, was considered for inclusion in the DSM-IV but currently resides in the appendix of disorders in need of further study as possible additions to the DSM-V, which is expected to be released in May 2013.

The key features of the major types of anxiety disorders are outlined in Table 2-2. Given the heterogeneity of anxiety as a topic, the aim of this section was to provide an overview of a working definition of anxiety and an overview of anxiety disorders in general. However, within stroke, generalised anxiety disorder, and post-traumatic stress disorder to a limited extent, have garnered the most attention. Issues associated with diagnosis and patterns of illness relevant to stroke are discussed in the following section.

Table 2-2 Key features of specific anxiety disorders

Disorder	Key Features
Panic disorder (with or without agoraphobia	- Recurrent unexpected panic attacks without any obvious situational trigger - Active avoidance of situations in which panic attacks are predicted to occur - Manifestation of physical symptoms of anxiety (e.g. sweating, palpitations, trembling, chest pain, nausea, dizziness)
Generalised Anxiety Disorder (GAD)	- Uncontrollable and excessive worry occurring more days than not, about a number of everyday, ordinary experiences or activities. Often accompanied by physical symptoms (e.g. headache or stomach ache) - Intolerance of uncertainty
Social phobia	- Excessive or unrealistic fear of social or performance situations - Intolerance of embarrassment or scrutiny by others
Specific phobia	- Excessive or unreasonable fear of a circumscribed object or situation, usually associated with avoidance of the feared object (e.g. driving, walking)
Obsessive compulsive disorder (OCD)	- Presence of obsessions; recurrent, unwanted and intrusive thoughts, images or urges that cause marked anxiety (e.g. doubts about actions, contamination, thoughts of injury) - Compulsions; repetitive behaviours or mental acts that are performed to reduce the anxiety generated by the obsessions (e.g. checking, washing or repeating)
Post-traumatic stress disorder (PTSD)	- Occurs after a traumatic event to which an individual responds with intense fear, helplessness, or horror; patients relive the event in memory, avoid reminders of the event, and experience emotional numbing and symptoms of increased arousal - Re-experiencing of trauma

Adapted from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)(American Psychiatric Association 2000)

2.3 Assessment of anxiety after stroke- Diagnosis and screening

Assessing anxiety in the stroke population, and indeed among many individuals with long-term conditions is challenging. First, it is important to highlight the difference between diagnosing anxiety and anxiety symptom screening. Diagnostic approaches rely upon professional evaluation typically by structured or semi-structured interviews using diagnostic criteria such as the current Diagnostic and Statistical Manual of Mental Disorders

4th edition (DSM-IV) (American Psychiatric Association 2000) or the International Classification of Diseases (ICD-10)(World Health Organization 1999). Several clinician-administered clinical interview instruments can be used to diagnose anxiety disorders. These include, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First *et al.* 2002), and the Anxiety Disorders Interview Schedule (ADIS-IV) (Di Nardo, Brown and Barlow 1994). Formal clinical diagnosis has implications in terms of management and treatment of an anxiety disorder. However, as will be discussed, the diagnostic criteria for anxiety amongst those with stroke can be complicated by a variety of factors including the somatic symptoms of stroke, age, and co-morbidity with other illnesses.

The diagnosis of anxiety disorders requires specialist mental health training that is labour intensive, time consuming, and access to such expertise may not always be readily available for stroke survivors. As a result, screening for anxiety symptom burden or the probability of an anxiety disorder by use of a rating scale, is routinely carried out as an alternative form of assessment in both clinical practice and research rather than in-depth diagnostic clinical interviewing. Screening is used to identify anxiety "caseness" and is usually a quicker way of assessing emotional state than an in-depth diagnostic interview. Even though screening lacks diagnostic capability, the level of anxiety symptom burden in individuals not deemed to have a disorder but identified with significant symptoms burden, has been found to be associated with similar levels of anxiety and worry to individuals diagnosed with an anxiety disorder (Diefenbach *et al.* 2003). It should be noted that regardless of whether anxiety screening (case finding) or anxiety diagnosis (case determination) is carried out, the term anxiety is used interchangeably for both, even though they are fundamentally referring to different concepts.

Current national clinical guidelines for stroke in the UK propose that all patients in the rehabilitation phase of stroke should be screened for anxiety by either asking the patient about their concerns, or by inquiring with a family member (Royal College of Physicians 2008). However this is more ambiguous than the guidelines suggested for post-stroke depression screening, whereby a screening protocol stratified by patient characteristics has been developed specifying appropriate depression scales for use (Stroke Improvement programme 2011b). It would not be possible to provide an exhaustive review of all available anxiety screening scales, however three have been validated within the

stroke population and are described below. A summary of findings from these validation studies can be found in Table 2-3.

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) is the most extensively used rating scale for screening anxiety symptoms in stroke survivors found in the published literature (Campbell Burton *et al.* 2012). This 14 item self-report scale only asks about psychological symptoms such as worry, restlessness, and feelings of panic associated with anxiety. This was an attempt to avoid confounding with somatic symptoms often present in those with long-term conditions and those of anxiety. The HADS can also distinguish between anxiety and depression and is not just a general measure of psychiatric distress. Overall, anxiety subscale scores range from 0 to 21, with authors recommending a score of 8-10 as indicative of possible anxiety, and ≥11 of probable anxiety. It has been suggested that using lower threshold cut-off score may be more appropriate when screening for anxiety in stroke patients (Bjelland *et al.* 2002), as this would lead to increased sensitivity in identifying individuals with substantial anxiety burden. However the focus on the sensitivity and specificity of scales also needs to take into account the issue of anxiety prevalence in the population. If prevalence is low, the positive predictive value of the rating scale decreases (Table 2-3), and while treatment would not be initiated solely based on the results of on a screening scale, rating scales are frequently used in research as a means of estimating prevalence. The HADS is discussed in further detail in chapter six.

The General Health Questionnaire (GHQ-28)(Goldberg and Hillier 1979), and the Beck Anxiety Inventory (BAI) (Beck *et al.* 1988) are two other scales whose validity within the stroke population has been assessed, although to a lesser extent. The General Health Questionnaire (GHQ) is a self-administered screening questionnaire aimed at detecting diagnosable psychiatric disorder. It focuses on an individual's inability to carry out normal 'healthy' functions, the appearance of new distressing phenomena, and the relationship between psychological illness and health. The GHQ-28 screens explicitly for four factors of psychological mood disorder of which one is anxiety. A score >5 on the GHQ-28 is indicative of anxiety "caseness". A large Australian study was carried out in a population based cohort study of all stroke cases who were four months post-stroke to validate the GHQ-28 against the DSM-III (Johnson *et al.* 1995) (Table 2-3). It found that a cut-off score of 4/5 had the best trade-off of sensitivity and specificity when screening for anxiety. However they

also noted that the sensitivity of the GHQ-28 was reduced if the prevalence of anxiety was low.

The BAI is a 21 item self report scale designed to measure the severity of anxiety-related psychic and physiological symptoms. Overall scores can range from 0-63, with a cut-off score of 8/9 indicative of mild anxiety, 16/17 moderate anxiety, and 26/27 severe anxiety. Attempts to validate its use in the stroke population have been carried out in only one small study with 44 individuals (Schramke *et al.* 1998), and it was against the DSM-III-R. The authors who used a cut-off score of 16 reported that the BAI was sensitive in identifying anxiety disorder but lacked specificity. As a result of the small sample size and low prevalence of anxiety disorders (6%), findings of this study are difficult to interpret.

Table 2-3 Summary of screening performance of anxiety rating scales validated in stroke populations for identification of current anxiety disorder

Author, Location	Diagnostic system/ screening instrument rating scale validated against	N	Time post-stroke	Anxiety Prevalence*	Rating Scale (range)	Cut-off Value	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
(Johnson *et al.* 1995), Australia	DSM-III Non hierarchical approach (PAS)	66	4 months	All anxiety:19% Agoraphobia- 18% GAD- 5%	GHQ-28 (0-7)	3/4 4/5 5/6	79 71 50	46 56 62	28 30 26	39 88 82
		93	4 months	All Anxiety:23% Agoraphobia-19% GAD-8%	HADS-A (0-21)	4/5 5/6 6/7	95 80 57	38 46 56	31 31 28	96 89 82
(O'Rourke *et al.* 1998), UK	DSM-IV (SADS)	105	6 months	All Anxiety: 12% Adjustment- 2% Agoraphobia- 7% GAD- 2% Specific phobia- 1%	HADS-A (0-21)	6/7 8/9 10/11	83 50 42	68 87 92	26 34 42	97 93 92
(Sagen *et al.* 2009), Norway	DSM-IV (SCID)	101	4 months	All Anxiety: 23% GAD- 6% OCD- 2% NOS-1% Panic (with agoraphobia)- 8% Panic (without agoraphobia)- 3% PTSD- 3% Social phobia- 3% Specific phobia- 9%	HADS-A (0-21)	≥3 ≥4 ≥5 ≥7 ≥8 ≥9 ≥10 ≥11 ≥12	96 83 78 70 52 39 35 35 26	55 65 72 83 90 95 96 99 99	39 41 44 55 60 69 73 89 86	98 93 92 90 86 84 83 84 82
(Bennett *et al.* 2006), UK	HADS-A ≥8	79	~1 month	Anxiety caseness: 22%	VAMS (0-800)	255/256	0.71	0.66	40	90

DSM-Diagnostic and Statistical Manual of Mental Disorders (3rd & 4th edition), GHQ-28- General Health Questionnaire-28, HADS-A Hospital Anxiety and Depression Scale, Anxiety Subscale, PAS- Psychiatric Assessment Schedule, SADS- Schedule for Affective Disorders and Schizophrenia, SCID- Structured Clinical Interview for DSM-IV GAD- Generalised anxiety disorder, OCD- Obsessive compulsive disorder, PTSD- Post-traumatic stress disorder

The Geriatric Anxiety Inventory (GAI) (Pachana *et al.* 2007) is a newer 20-item self-report or clinician-administered scale that measures dimensional anxiety in elderly people. It consists of 20 "Agree/Disagree" items designed to assess typical common anxiety symptoms. The measurements of somatic symptoms with the instrument are limited, in order to minimize confusion between symptoms common to anxiety and general medical conditions. Research about the appropriateness of the GAI in stroke patients age 65 years and older receiving inpatient rehabilitation is currently underway. It is expected that this study will be completed in September 2013 (Stroke Association Current Research Projects and Programme Grants, June 2011).

The Wimbledon Self Report Scale (Coughlan and Storey 1988) is another scale which could have potential in identifying possible cases of anxiety. The Wimbledon scale consists of 30 items designed to measure general mood disturbance in people with neurological or major physical illness. It was designed to identify patient feelings and avoids enquiry about somatic symptoms, memory and concentration problems and ability to participate in or enjoy former activities. It also seeks to provide clinicians with knowledge of which adverse feelings a patient is experiencing, which is useful to know regardless of whether or not these feelings comprise a clinical level of psychological disturbance. Its sensitivity and specificity for identifying possible cases of anxiety after stroke has not been evaluated, however it has been found to be sensitive in screening for major and minor depression, when validated against a structured clinical interview (Lincoln *et al.* 2012). However the sample consisted of only eight stroke patients and the confidence intervals were wide so findings should be interpreted with caution

All the aforementioned scales can be used in individuals without communication problems, however many stroke survivors suffer from aphasia, or other language deficits. It is worth noting that currently the visual analogue mood scale (VAMS) (Stern *et al.* 1997) is the only scale whereby validation has been attempted amongst stroke survivors with communication problems. The VAMS was validated against the HADS-A that used a cut-off of ≥8 to assess anxiety 'caseness' (Bennett *et al.* 2006) (Table 2-3). While this appears to be a promising tool for use in this subgroup of stroke survivors, further evaluation of cut-off scores and assessment against a clinical diagnostic criterion are needed.

Assessing anxiety in stroke patients is important because it identifies individuals with potential problems and allows for an understanding of the nature of the psychological condition in order to plan treatment and monitory changes over time (Lincoln *et al.* 2012). The overall findings suggest that the standard cut-offs of the validated scales may not be appropriate when screening for anxiety after stroke. Sensitivity of both the HADS-A and the GHQ-28 were higher when lower threshold scores of the respective scales were used. The disadvantage however, is that there was a substantial trade-off in specificity and the positive predictive value of the scales when using the lower cut-off scores were not always much higher than the probability of having anxiety in the populations examined. If the aim is to identify as many individuals as possible who may be at risk for a serious anxiety condition then using a lower threshold score on the validated anxiety screening scales is appropriate. However, this approach may be inefficient where access to psychological services are scarce, which is often the case for stroke survivors (National Audit Office 2010). In summary, no clear trend has emerged from the existing studies suggesting further evaluation is needed for guidance in terms of assessing anxiety after stroke when using methods other than diagnostic interview.

2.3.1 Issues with diagnosis and screening for anxiety

Diagnosing or screening for anxiety after stroke are not straightforward processes. One of the major issues concerning both approaches is criterion contamination, which refers to the overlap between the physical (and emotional) symptoms of co-morbid disease. This overlap makes it difficult to determine which symptoms should be attributed to which condition of interest (Jeste, Blazer and First 2005). For example insomnia, poor concentration, and low energy may be observed after stroke. The cause of such symptoms could be attributed to either stroke, anxiety or both. This limitation further highlights the need for in-depth diagnostic inquiry should an individual screen positive for anxiety "caseness".

Another challenge with establishing anxiety in stroke survivors or individuals with long-term conditions, is that symptom presentation may differ in these groups compared with its presentation in the general population. While evidence is not available about the manner in which stroke patients present when experiencing anxiety specifically, a focus

group discussion conducted with General Practitioners (GPs) found that general outpatients, some of whom had serious medical conditions, tended to emphasise the physical as opposed to psychological symptoms of their (van Rijswijk *et al.* 2009). Also factors such as patients age (e.g. being older), having limited verbal ability, using different language to describe symptoms (e.g. "concerns" rather than "worry"), and difficulty remembering or identifying symptoms increased the difficulty in recognising an anxiety disorder or symptoms burden (van Rijswijk *et al.* 2009). While stroke survivors share many of these characteristics and it is plausible that similar patterns occur in this group, several limitations in the study design need to be taken into account. To start this was an explorative study with only 23 Dutch GPs, many of whom expressed strong reservations about the validity and usefulness of the DSM-IV concepts of anxiety and depressive disorders. Whether these views are generalizable to clinicians charged with caring for stroke survivors in other settings is unknown.

Another issue that could occur when screening for anxiety is deciding how to distinguish between an emerging disorder and non-pathological anxious avoidance. For example, a review of studies examining anxiety disorders in older adults concluded that both patient and clinicians misattribute fear and anxiety symptoms to the normal process of aging (Wolitzky-Taylor *et al.* 2010). While no studies have been carried out in stroke patients on this topic, a possible example of such a misattribution would be a new-onset of agoraphobic disorder being less obvious, and as a result undiagnosed, in a stroke survivor who was not mobile and left their house less frequently. Similarly social phobia could be attributed to diminished physical abilities, such as muscle weakness or vision problems that could make a stroke survivor understandably reluctant to interact with others. Furthermore, primary care is where many individuals present with mental health problems. However, practitioners in these settings have expressed deficiency in their knowledge of specific anxiety disorders, and reported difficulties accessing specialist mental health services (van Rijswijk *et al.* 2009) (Wolitzky-Taylor *et al.* 2010).

Discriminant validity is also an issue when trying to assess the presence of mental health disorders. The DSM uses a categorical classification system that divides mental disorders into types based on criteria sets with defining features. The same approach is also used when applying screening scales, in that an individual may be deemed "anxious" if they

score above a given threshold. This method of organising and classifying information into unique categories is similar to the fundamental approach used in all systems of medicine. The categorical approach to classification attempts to present all members in a diagnostic class as homogenous. However homogeneity of presentation within anxious patients is likely to be an exception rather than the norm, with individuals who share a diagnosis having dissimilar defining features of the disorder. Advantages of categorical systems are that they facilitate treatment decisions for clinicians by providing clear guidance for determining when to intervene with an intervention (Kessler 2002). They aid researchers in quantifying the phenomenon of interest, which is important for needs assessment research or establishing the extent of a problem. The categorical approach also provides information about lifetime occurrence and makes it possible to ask about discrete syndromes and obtain information about onset and chronicity. The drawbacks of a categorical system however, include measurement error arising from uncertainties about the threshold definitions, such as whether the features of a given disorder are sufficient in number, duration or severity to warrant a DSM diagnosis (Brown *et al.* 2001b). There is also loss of important information regarding the severity and associated features of disorders (Kessler 2002), which can lead to a high prevalence of individuals being assigned to the "not otherwise specified" category, or diagnostic unreliability (Brown *et al.* 2001a).

A dimensional system of organisation for determining anxiety distress has been suggested (Brown and Barlow 2005; Brown and Barlow 2009). Dimensional systems classify clinical presentations based on quantification of attributes rather than assigning them to categories and are useful for describing phenomena, such as anxiety, which are distributed continuously and do not have clear boundaries. While dimensional systems increase reliability and communicate more clinical information because they report clinical attributes that might be sub-threshold in a categorical system, they also have many limitations (American Psychiatric Association 2000). Dimensional descriptions are less clear-cut and are more difficult to understand. There are currently no agreed criteria for implementing a dimensional approach for the DSM, however research continues and there may be a greater adoption of dimensional approaches with future versions of the DSM. The same issue applies when using anxiety screening scales. To start, epidemiological studies would need to be conducted to determine normative scores in the stroke population, and then the

clinical significance of the scores would need to be established. Whether it is making a clinical diagnosis of an anxiety disorder, or using a rating scale to determine anxiety caseness, there is a substantial reliance on clinical judgement.

The final limitation that will be discussed in this section is a practical concern, especially in the case of screening. Staff require training and support, and the multi-professional nature and fast pace of stroke care may result in lack of clarity as to who is responsible for completing screening (Morris *et al.* 2012). Despite guidelines advocating that all patients be screened for anxiety, national audit data reveal that this does not occur for over a third of stroke patients, and that psychological support services were rated as the least satisfactory aspect of long-term care after stroke (National Audit Office 2010). Several individual factors (e.g. knowledge of anxiety and the assessment process, knowledge about patients, awareness of guidelines, and beliefs about effectiveness of the screening tool) and organisational factors (e.g. support for colleagues, integration of screening assessment into the job role, and provision of time) have been shown to affect the ability to accurately screen for mental health problems after stroke (McGinnes 2009). An intervention study, designed to improve rates of screening for anxiety and depression, concluded that major improvements would require systematic protocols, and need to account for complex environmental factors in order to be successful (Morris *et al.* 2012).

2.4 Anxiety after stroke and co-morbidity with other mental health conditions

It is well established that anxiety and depression are strongly co-related. Epidemiological research has shown that co-morbidity is the norm rather than the exception, with co-morbidity rates ranging from 25% to 70% (Cairney *et al.* 2008; Moffitt *et al.* 2007). There is still much debate as to whether frequent co-morbidity is a result of co-occurrence of two commonly occurring illnesses or reflects one of them being either an epiphenomenon or a complication of the other. For example, some have suggested that GAD would be better conceptualised as a prodrome, residual or severity marker of a major depressive episode as opposed to an independent disorder (Noyes *et al.* 1992; Clayton *et al.* 1991). In contrast other studies have found support for the separation of anxiety and depressive states (Prusoff and Klerman 1974; Brown, Chorpita and Barlow 1998).

The high level of co-morbidity of anxiety and depression, and possibility of uncertainty of the strict categorical classification of anxiety and depression, has led some to argue for the inclusion of a "mixed anxiety-depressive" category as a distinct diagnostic category in future versions of the DSM. The belief is that it could have more heuristic and clinical utility. While this may be the case, there would be some drawbacks to this new category. For example some have argued that a mixed category could overlap too much with other anxiety disorders, or that it could become a "wastebasket" category and subsequently discourage more careful diagnosis of anxiety problems (Liebowitz 1993).

The topic of mixed-anxiety and depression will undoubtedly have relevance in the stroke population. It is estimated that one-third of stroke patients have depression at some time after stroke (Hackett *et al.* 2005). Perhaps due to the hierarchical diagnostic principles that were in place until the introduction of the DSM-III-R that precluded the diagnosis of anxiety in the presence of a mood disorder, the association between anxiety and depression in stroke has been given little consideration. Even under the current DSM-IV, individuals who experience generalised anxiety disorder during the course of a mood disorder are not diagnosed with anxiety, indicating lingering remnants of the hierarchical approach to diagnosis. Co-morbidity is of significance as it has been found to decrease social function, and increase somatic symptom severity of both anxiety and depression, increase the risk of suicidality relative to either condition occurring in isolation, and impede treatment responsiveness to therapy (Lenze *et al.* 2000; Wolitzky-Taylor *et al.* 2010).

Also of interest is the chronology of anxiety and depression within stroke survivors. Longitudinal studies in non-clinical younger and older adult samples suggest that anxiety disorders often precede depressive disorders (Michael, Zetsche and Margraf 2007). Additionally, anxiety tends to be chronic without spontaneous remission, whereas depression has been found to be episodic and in some instances recurrent (Lenze *et al.* 2005). This was confirmed in a review of depression after stroke that found that depression resolved spontaneously within several months in the majority of stroke survivors (Hackett *et al.* 2005). Findings about anxiety after stroke are discussed further in chapter four.

How anxiety and depression are classified and researched in both the general population and within stroke will remain a topic of debate and discussion for some time to

come. At the time of writing this thesis, no conclusion had been reached on the topic of formally recognising a mixed anxiety-depression category.[1]

2.5 How anxiety will be conceptualised in this thesis

The concept of anxiety disorders and their symptomatology is multifaceted. The complexities include the large number of different anxiety disorders, widespread comorbidity, a partial lack of symptom specificity from disorder to disorder, and the influence other external factors may have on its manifestation. However, despite the limitations of the DSM, its definition of anxiety disorder will be used. Additionally anxiety symptoms or "caseness", as defined by a rating scale, will be deemed to be of equal significance.

2.6 Aetiology of anxiety after stroke

Little research has been carried out into investigating the aetiology of anxiety after stroke. However, biological and psychological theories have been used in the context of determining causes of mood disorders post-stroke. Their applicability to anxiety are discussed below.

2.6.1 Lesion location hypothesis

The biomedical model approach of conceptualising disease, focuses on the pathology, biochemistry, and physiology of a condition, and does not take into account individual and social factors that may be relevant when dealing with long-term conditions (Barondess 1979). In line with this approach is the lesion location hypothesis, which has been applied in a very limited capacity in the investigation of anxiety after stroke. The lesion location hypothesis proposes that post- stroke mental health problems are caused by focal damage to specific areas in the brain. Investigation of this hypothesis for anxiety after stroke has produced mixed findings. Some studies have indicated that anxiety is associated with left hemisphere lesions, even after taking into account other factors such as age, gender, cognitive processing ability, and distance of the lesion from the anterior pole of

[1]. April 30, 2012 update on the American Psychiatry Association website states that mixed anxiety and depression will be allocated to section III in the DSM-V, which are conditions that require further research, http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=407#

either brain hemisphere (Barker-Collo 2007a; Sharpe *et al.* 1990). Other studies have looked at anxiety and co-morbidity with depression and reported that anxiety alone is associated with right hemisphere lesions, but is associated with left hemisphere lesions when co-morbid with depression (Astrom 1996; Robinson 2006). A study carried out in 277 stroke patients reported that lesions in the anterior circulation region were more likely to have GAD relative to those without lesions in that area (Leppavuori *et al.* 2003). However, this study did not indicate the hemisphere where the lesions were located. Another large study in 185 stroke inpatients reported that amongst those with left hemisphere lesions, individuals with GAD alone had significantly fewer cortical lesions than those with co-morbid GAD and depression (Robinson 2006). On the other hand, amongst patients with right hemisphere lesions, those with GAD alone had significantly higher frequency of posterior lesions as compared to patients with neither anxiety nor depression. The studies suggest an interaction between the existence of GAD and depression, with co-morbidity being associated with left hemisphere lesions and anxiety alone associated with right posterior lesions (Table 2-4).

Table 2-4 Summary of studies proposing lesion location associated with anxiety after stroke

Study & Location	N	Region associated with anxiety
(Barker-Collo 2007a), New Zealand	73	Left hemisphere lesions associated with higher levels of anxiety symptoms on the Beck Anxiety Inventory
(Sharpe *et al.* 1990) UK	55	Left hemisphere lesion volume significantly associated with anxiety symptoms on the HADS-A
(Robinson 2006), USA	185	GAD alone associated with right hemisphere posterior lesions Co-morbid GAD and Major depression associated left hemisphere lesions
(Astrom 1996), Sweden	71	GAD alone significantly associated with right hemisphere lesion Co-morbid GAD and Major depression associated with left hemisphere lesion *Associations no longer significant after three months post-stroke
(Leppavuori *et al.* 2003), Finland	277	Anterior circulation region associated with GAD, hemisphere not indicated

The lesion location hypothesis has been tested more extensively in the assessment of depression after stroke. A systematic review that included 48 studies, of which 35 were included in a meta-analysis, concluded there was no support for the hypothesis that the risk of depression after stroke was associated with the location of the brain lesion even when taking into account time since stroke (Carson *et al.* 2000). Currently there is also no support for the lesion location hypothesis for anxiety after stroke.

2.6.2 Psychological models

The limitations of the lesion location hypothesis and the fact that post-stroke mental health problems are associated with a range of psycho-social factors, has lead some researchers to theorise about psychological aetiologies of not only depression after stroke but also anxiety. One hypothesis proposed that anxiety after stroke could be caused by projected hostility with resulting fear of abandonment, fear of a medical emergency, need for attention and control over others or feeling of helplessness (Binder 1984).

A systematic review on self-efficacy, which is "*the beliefs people have about their capabilities to produce a designated level of performance that exercise influence over events that affect their lives" (Bandura 1994)*, concluded that self-efficacy was inversely associated with depression, neuroticism, and coping post-stroke (Jones and Riazi 2011).

Cognitive theory (Beck 1985), has also been explored as a means of understanding mental health distress after stroke (Nicholl *et al.* 2002; Lincoln and Flannaghan 2003), and forms the foundation of cognitive-behaviour therapy which is discussed in section 2.11.2. The cognitive model of emotional disorders proposes that three levels of cognition are responsible for the aetiology and persistence of anxiety and depression (Clark and Beck 2010). At the core are "*schemas*" which are used to identify, interpret, categorise and evaluate an experience (i.e. a health threat). Attitudes and beliefs form the content of these schema and they may have pre-existed prior to the onset of the threat or developed there after. Once activated from incoming stimuli (i.e. an illness), schema can give rise to "*biased information processing"* which results in increased attention to cues seen as threatening or dangerous and feelings of helplessness. This selective information processing can lead to increased levels of dysfunctional anxiety. The dominance of this negativity bias ultimately results in "*negative automatic thoughts"* images and memories that perpetuate a subjectively adverse emotional state.

The common-sense self regulatory model (CSM) (Leventhal, Nerenz and Steel 1984) has been used extensively across a range of disease groups to identify the nature and content of illness schema, with the view that insight into these schema may assist in developing interventions that minimise emotional distress during chronic illness. A description of the CSM and its use in stroke receives further attention in chapter three.

2.7 Prevalence of anxiety disorders and symptoms after stroke

Globally anxiety disorders are the most commonly observed type of mental health condition with 12-month prevalence estimates ranging between 3% and 19%(Kessler *et al.* 2009; Somers, Goldner and Waraich 2006; Wittchen and Jacobi 2005). However many of these studies excluded older adults over the age of 65 years, used different operational definitions of anxiety, or excluded certain types of anxiety disorders such as PTSD, making these findings non-generalisable to the stroke population. Furthermore, early theories

contended that older adults generally had more advanced coping strategies and were less likely to suffer from anxiety disorders (Regier *et al.* 1988; Flint 1994). Initial studies into the prevalence of psychological problems post-stroke seemed to support this assumption, finding that the prevalence of anxiety after stroke was between 1% and 5% (House *et al.* 1991; Morris, Robinson and Raphael 1990). This was in sharp contrast to later studies that found post-stroke anxiety prevalence rates as high as 20% or 30% (Astrom 1996; Leppavuori *et al.* 2003). The large range in prevalence estimates supported the need for a systematic review to establish a reliable quantitative estimate of this phenomenon in stroke survivors. Such work was subsequently carried out as part of this thesis and is discussed in detail in chapter four.

2.8 Risk factors for anxiety after stroke

In the general adult population there are numerous factors that have been found to increase the risk of having anxiety (Table 2-5) (Vink, Aartsen and Schoevers 2008; Michael, Zetsche and Margraf 2007). These include, but are not limited to, being female, younger age, and having limitations in activities of daily living. However much of the research upon which these findings are based has excluded older adults who have a greater chance of having a significant co-morbid physical illness such as stroke. When younger and older individuals have been compared, there is some evidence to suggest there may be differential risk factors for anxiety across the lifespan. For example, one study that compared older (60 years and older) with younger individuals found that social support and earlier traumatic event exposure were associated with anxiety for both groups. However lower income was associated with anxiety for older adults but not younger adults, whereas female gender was associated with anxiety in younger adults only (Vink *et al.* 2009).

Amongst stroke survivors a small study found that within the first month after stroke living alone was a significant risk factor for developing GAD, however by three years post-stroke level of independence in activities of daily living and having few social contacts became significant predictors of GAD (Astrom 1996). Another study reported that denial of stroke in the acute phase was associated with the development of anxiety at three month follow-up (Ghika-Schmid *et al.* 1999). These results should be interpreted with caution as the sample size for both studies was small and they had substantial loss-to follow-up. As

such, they could be biased and non-generalisable. Others have proposed that psychological reactions to stroke are in large measure determined by an individual's pre-morbid thought processes, personality, and coping mechanisms (e.g. thoughts and behaviours employed by an individual to manage stressful situations) (Folkman and Lazarus 1988). Individuals who are predisposed to feeling distressed and who tend to be highly emotional in reaction to stress, may be more likely to interpret or appraise their condition as overly stressful and to feel that they lack control over it. Hence the ability to cope with a stroke per se would be dependent on the appraisal of the event as stressful and on the capacity to utilise effective strategies in changing one's relationship to the situation and regard it as manageable (Folkman and Lazarus 1988).

Table 2-5 Risk factors for anxiety in the general adult population

• Female	• Hypertension
• Younger age	• Cognitive impairment
• Physical limitations in activities of daily living	• Dysfunctional coping
• Severe chronic medical conditions	• Previous mental health problems
• Single/divorced/ separated	• Lack of social support
• Lower education	• Stressful life event
• Poor self perceived health	• External locus of control

A qualitative study found that three main themes emerged as being associated with anxiety in stroke survivors (Lander 2009). The first was feelings of vulnerability due to physical impairment and other people, and discrimination in the sense of being ignored or avoided by others or being unable to access facilities. Perceptions of being dependent or having loss of autonomy were also cited as anxiety provoking. Lastly failing to meet expectations based on pre-stroke beliefs resulted in distress. When an individual was unable to perform tasks they thought they should be able to, it led to them feeling embarrassed and stupid, and some could not accept their current impaired state as being a reflection of their true self. The stroke rehabilitation pathway itself has been found to be a major contributor of distress (Ch'ng, French and McLean 2008). The post-stroke prognosis is generally uncertain, and individuals may initially have a sense that they can make a full

recovery. The vague expectations provided by healthcare professionals and the inability to return to their pre-stroke state can be anxiety provoking.

2.9 Impact of anxiety after stroke

The assessment of anxiety after stroke is important not only because of the distress it causes but also because it is associated with a wide range of outcomes. However its impact has yet to be studied extensively. Limited information from one U.S. based study in a sample of 142 stroke survivors recruited whilst in hospital found that depression after stroke was more severe and longer lasting in those with co-morbid anxiety when assessed at three month to two year follow-up post stroke (Shimoda and Robinson 1998). Additionally this study also found that stroke patients with co-morbid anxiety and depression had higher levels of impairment in activities of daily living, more cognitive impairment and fewer social ties than those with depression alone (Shimoda and Robinson 1998). Findings from this study should be interpreted with caution as it excluded individuals with severe comprehension deficits and the study sample consisted primarily of individuals from a low socioeconomic background. Additionally, the associations between anxiety and depression which were described were only carried out for individuals who at study onset were found to have anxiety. As this was only a small group of individuals follow-up analyses were likely underpowered to identify other possible negative consequences of anxiety after stroke.

To date, no studies have assessed the economic cost associated with anxiety after stroke. However, in the general population it is known that individuals with anxiety are often high consumers of primary care services, and can make up a large proportion of the people who overuse primary care for only vaguely defined physical complaints (Kessler and Greenberg 2002). The significant burden that anxiety alone imposes on individuals, their carers, the health service, and communities globally is recognised. In 2007, the overall cost of anxiety health services in England were estimated to be £1.2 billion, with lost employment costs (indirect cost) due to anxiety bringing the total to £8.9 billion (McCrone *et al.* 2008). The indirect costs were only calculated for individuals under 65 years of age and did not take into account the financial cost to carers and partners, or loss of independence that can accompany anxiety disorders. Within the next 15 years these cost are projected to rise to £2 billion and £14.2 billion respectively.

To date no studies have investigated the combined economic effect of anxiety after stroke. However, one U.S. based study assessed the economic impact of anxiety and depression in a large managed care chronic obstructive pulmonary disease (COPD) population (Dalal *et al.* 2011). It reported that COPD patients with co-morbid anxiety or depression were more likely to be hospitalised (OR=1.77, p<.001) or visit an emergency room (OR=1.60, p<.001) when compared to those with COPD only. Furthermore medical and pharmacy costs were 30% greater (p<.001) in the co-morbid group. Disaggregated results for anxious, depressed, and co-morbid anxious and depressed COPD patients were not provided.

The very limited evidence suggests that anxiety may place a substantial additional economic burden on stroke survivors and their family. This is especially relevant given that a quarter of strokes occur in people of working age, many of whom have been found not to return to work (Gabriele and Renate 2009). With increases in the post-stroke survival rate, it is likely that these costs will continue to increase due to a 'cohort effect' of the increased likelihood of lifetime prevalence of anxiety disorder that has been observed by using retrospective age-of onset reports that estimated lifetime prevalence as a function of age (WHO International Consortium in Psychiatric Epidemiology 2000). Within stroke and other long-term conditions it is proposed that anxiety has a negative influence on quality of life (Ahlsio *et al.* 1984). For example a study in cardiovascular patients found that anxiety had a greater role on quality of life even after adjusting for disease severity and physical disability (Giardino *et al.* 2010). However this was a cross-sectional study, so the directionality of the association between quality of life and anxiety cannot be established.

2.10 Approaches to treatment and management of anxiety after stroke

There are various treatment options for anxiety disorders or sub-syndromal symptoms available for the general population. Currently the evidence base for treating anxiety specifically within the stroke population is limited (see Chapter 5). In the UK the Stroke Improvement Programme has adapted the stepped care approach to treating and managing anxiety as recommended by NICE for the management of anxiety disorders in the general adult population, and the Department of Health's Improving Access to Psychological Therapies (IAPT) programmes (National Institute for Health & Clinical Excellence 2011).

The current evidence-based guidelines for anxiety after stroke deal primarily with screening and in particular during the acute phase after stroke, although it is expected that anxiety guidelines to be published in 2012 will be significantly expanded upon (Royal College of Physicians 2008). Anxiety can be chronic and it is anticipated that more emphasis on long-term stepped-care follow-up will be advocated in the 2012 the Royal College of Physicians national clinical guidelines for stroke.

The stepped care approach is based on two core principles. The first being that the interventions on offer should be the 'least restrictive' that will be effective, and the second is that there should be self-correcting monitoring and feedback systems to ensure individuals are stepped up to more intensive interventions if they are not obtaining sufficient benefit from the initially offered treatment (National Institute for Health & Clinical Excellence 2011). Specific interventions on offer will be described in the next section.

Three levels of care are identified within the National Stroke Improvement Programme (Figure 2-1) (Stroke Improvement programme 2011b). At the first level (level 1) it recommends all patients be assessed for mood disorder using a simple brief standardised measure, such as the HADS. At this stage some individuals may be experiencing difficulties coping or with their perceived consequence of stroke on their lifestyle or identity. However these feelings are not deemed to impact their ability to engage in rehabilitation. In addition to administering a rating scale, assessment should be followed up with an interview, as scales may be unreliable or miss certain aspects of distress. The team providing care or follow-up services should be sufficiently competent to provide low levels of psychological care and information about informal support or professional help when required.

Individuals at level 2 are those with mild to moderate psychological symptoms that interfere with the rehabilitation process. A higher intensity psychological intervention may be offered or even pharmacological medication considered. Interventions administered at this level could be provided by non-specialist staff with supervision by a clinical psychologist or psychiatrist. Individuals with a diagnosed severe and persistent anxiety disorder are considered level 3. Risk for self neglect or self-harm should also be evaluated. Those considered level 3 require the intervention of clinical psychologist with expertise in stroke and/or a psychiatrist.

Systematic research of the effectiveness of the stepped care approach has been based primarily on depression studies (National Institute for Health & Clinical Excellence 2011). Evidence of the use of this model in treating anxiety disorders is novel and somewhat limited. Where patients with anxiety have been involved in stepped care evaluation studies, they have tended to include primarily individuals with GAD as a secondary disorder, and in certain instances have explicitly excluded individuals with certain types of anxiety disorders such as PTSD and OCD (Richards and Suckling 2009; Richards and Borglin 2011; Clark *et al.* 2009). The pilot IAPT programme that received over 7000 patient referrals found that 55% of individuals who attended at least two sessions (including the assessment interview) were no longer anxious, as determined by a score below a pre-determined threshold on either a depression or anxiety rating (Clark *et al.* 2009). While this was the largest evaluation of the stepped care IAPT programme, these findings have several limitations. This was an observational study with no control site, so it is uncertain how many individuals would have improved through spontaneous remission of psychological symptoms. Additionally, complete case data was unavailable for over half of the individuals who were assessed at study onset. As a result it is unclear how many individuals would complete the treatment and meet the criteria for recovery after therapist contact had ended, which could lead to biased findings. It was theorised that some of the patients who completed the programme contact in the first year could have been more likely to recover, thereby leading to an inflated success rate (Richards and Borglin 2011). The high level of attrittion also highlights the need to improve patient engagement once a referral has been made. Finally, the pilot sites were highly scruitinised during their first year of operation, hence the extent to which they functioned in a 'business as usual' fashion could be called into question.

Unlike other established treatment options such as cognitive behavioural therapy which is described in the following section, the evidence base for using the IAPT stepped care model is limited. However, despite the limitations of the research, the general concensus has remained that stepped care is effective (Richards and Suckling 2009; National Institute for Health & Clinical Excellence 2011) . Once it becomes more established and available across the UK, its effectiveness for the stroke population will need to be evaluated.

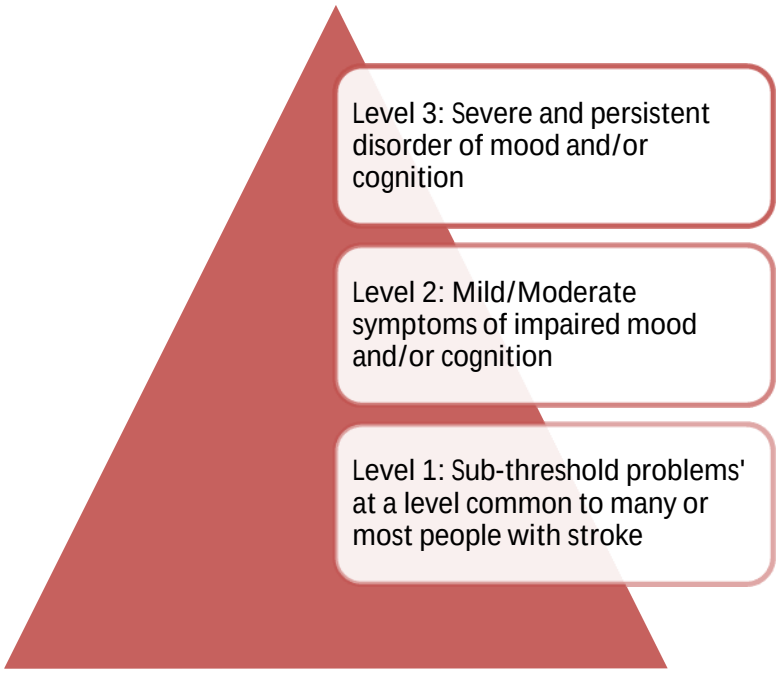


Figure 2-1 Stepped care model for psychological interventions after stroke (Adapted from IAPT model)(Stroke Improvement programme 2011b)

The majority of the IAPT services are available only in clinics and this may not be the best way to meet the needs of stroke survivors. The original pilot sites for the IAPT programme found that encouraging self-referral as opposed to GP-only referrals improved access for underrepresented groups and individuals who had been experiencing psychological distress for longer periods of time (Clark *et al.* 2009). Ideally post-hospital psychological care would be stroke specific, provided under the guidance of a clinical psychologist and available in the community. However, the on-going shortage of such staff as identified in recent national audits, mean that organisations will have to provide additional professional training for staff, so they can effectively contribute to the provision of these services.

2.11 Overview of psychological & other therapies

Various forms of psychological therapies that could be incorporated into the stepped care approach, are available for treating anxiety. A qualitative study exploring barriers to antidepressant use in a cohort of older adults age 60 years and older, found that psychological therapy was generally preferred over the use of antidepressant drugs (Givens,

Datta and Ruckdeschel 2006). This preference for psychological care centred around concerns about fear of drug dependence, prior negative experiences with antidepressants, believing antidepressants prevented the expression of natural emotions, or resistance to viewing their psychological symptoms as a medical illness (Givens, Datta and Ruckdeschel 2006). These findings are limited in that the study did not obtain views from younger individuals, the participants had recently taken part in a depression treatment delivery trial and therefore may have had substantially different views about psychological treatment and the study demographics were such that findings may not be transferable to other locales such as the UK. Additionally, patients may be reluctant to pursue pharmacological therapy as they may already be taking several medications and additional drug therapy could be contraindicated. According to the stepped care approach to treating mental health conditions, psychological interventions can be divided into two streams: Low-intensity and high intensity.

2.11.1 Low intensity psychological interventions

Low-intensity interventions are embedded into service provision framework as a means of increasing access to psychological treatment for people experiencing mild to moderate anxiety (or depressive) disorders. They are integral to the stepped-care approach and provide many of the least restrictive treatment options for people at levels one and two. Many of these low intensity interventions are based on the principle of cognitive behavioural therapy which is described in the following section. While there is no agreed definition on exactly what constitutes a low intensity intervention, there is a consensus that they generally require less healthcare professional resources and time.

Guided self –help (a self administered book, workbook, or multimedia material with limited support from healthcare professional or paraprofessional such as a wellbeing practitioner for three to 10 sessions), *non-facilitated self-help* (a book or workbook within minimal therapist contact), and *psychoeducational groups* (e.g. didactic teaching delivered to a group, may last up to six weeks) are the low-interventions with the largest evidence base (National Institute for Health & Clinical Excellence 2011).

While guided and non-guided self-help have shown moderate effects in treating anxiety with no apparent indication of harm, there are a few drawbacks for these

interventions (National Institute for Health & Clinical Excellence 2011). There is ambiguity about the best method of delivering guided and non-guided self-help. Participants may need to use written material or a computer and for stroke patients this could prove impractical. In terms of cost, guided self-help may be the most costly option depending on the number of sessions. Additionally, written self-help resources require a certain level of literacy, and few have been translated into other languages. Overall the quality of evidence in the NICE review was rated as low due to inconsistencies in the comparator groups (e.g. some studies using wait-list controls and others using treatment as usual) and some of the trials included individuals with mixed anxiety disorders rather than specific disorders (National Institute for Health & Clinical Excellence 2011) . The effect observed for psycho-educational interventions is classified as small, and there is a lack of information regarding harmful outcomes or programme discontinuation. The overall quality of the evidence was deemed low to moderate due to one of the clinical trials that formed the evidence based being quasi-experimental (National Institute for Health & Clinical Excellence 2011).

2.11.2 High intensity psychological interventions

High intensity psychological interventions are commonly used for people with moderate or severe anxiety, and people with these disorders generally prefer such treatments to medication (Prins *et al.* 2008).

The most commonly applied and researched high intensity psychological intervention is cognitive behavioural therapy (CBT). It is based on the premise that it is possible to adjust a person's thoughts, beliefs, attitude and expectations (cognitions) and manner of conducting oneself (behaviours). It is 'present-centred' and directs the participant to identify the current issues that are causing them distress, with the support of a trained psychological practitioner. Individuals talk about their specific problems in a structured manner with their therapist and may be given homework in the form of activities to complete before their next session. CBT is characterised as structured, goal-oriented and time-limited (approximately 10-12 sessions) (Beck 1997). CBT for anxiety in the stroke population has not been evaluated, however it has been for post-stroke depression with no evidence of benefit (details provided in chapter five) (Lincoln and Flannaghan 2003). It has been suggested hat augmenting CBT with any of the following: motivational interviewing (a

collaborative person centred form of guiding to elicit and strengthen motivation for change) (Miller and Rollnick 2009); grief counselling; or executive skills training could prove useful within the stroke population as it would address some of the special needs observed in this population (Broomfield *et al.* 2011). This theoretical hypothesis shown in Figure 2-2 was made specifically regarding depression post-stroke. Given the substantial co-morbidity with anxiety, there is reason to believe this model could be equally as useful for addressing anxiety after stroke as, CBT has been found to be effective in treating anxiety in the general population (National Institute for Health & Clinical Excellence 2011). However this model has not been empirically tested so further work is needed.

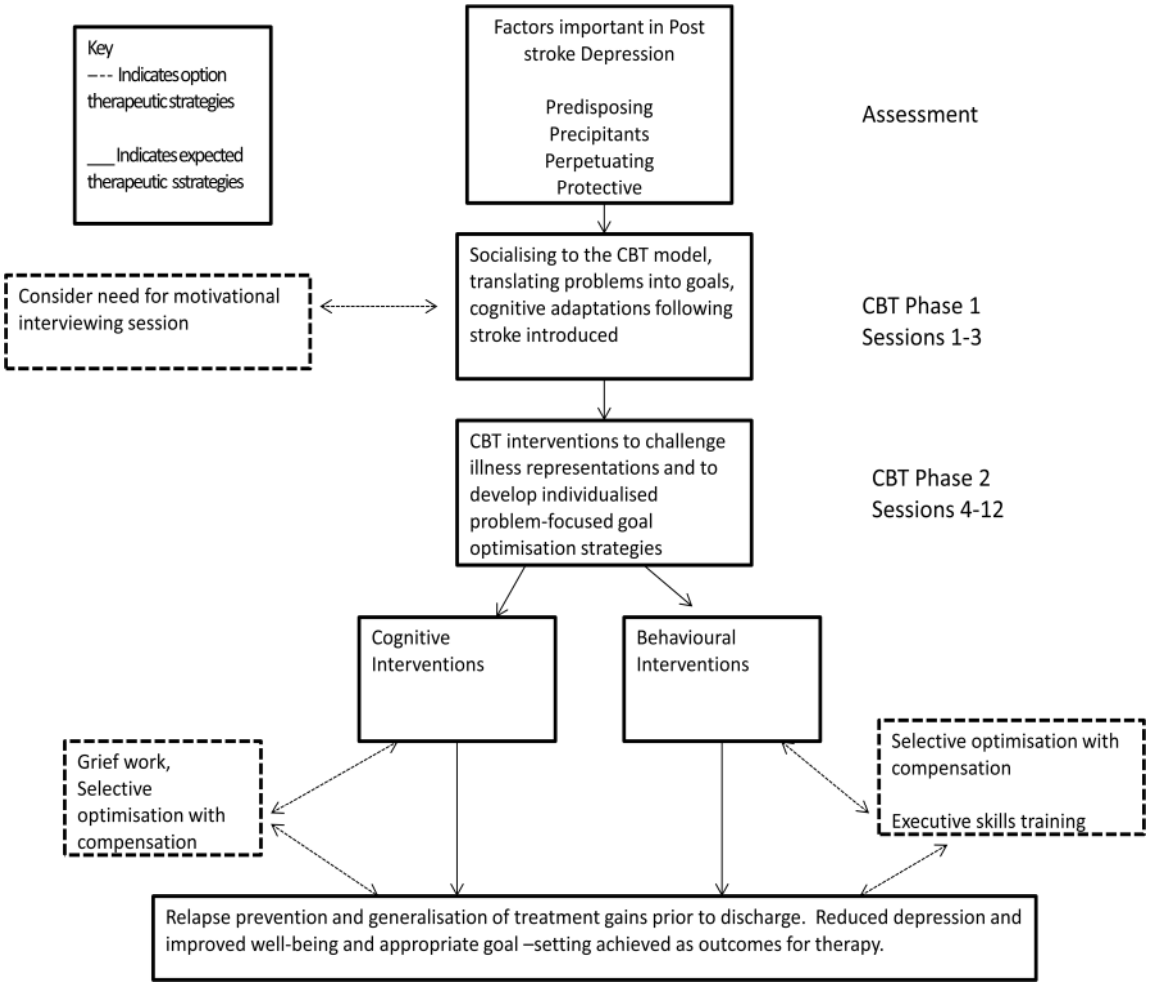


Figure 2-2 Illustration of augmented, individually tailored CBT for depression after stroke

2.11.3 Other therapies

The evidence base for other anxiety-related treatments has not been established, yet the stepped care approach takes into account patient choice and preference and other forms of therapy can be considered. An exhaustive account of all alternate interventions will not be provided, however a systematic review of over 34 complementary interventions found that therapies such as exercise training, which may act as a buffer for stress or trigger the release of monoamine neurotransmitters, and relaxation therapy, which teaches individuals to recognise the symptoms of anxiety and respond to them with a technique that reduces arousal, have been found effective for treating anxiety (Jorm *et al.* 2004).

2.12 Overview of pharmacological therapies

Patient preference is an important component of the stepped care approach. Individual motivation or inability to engage with treatment (e.g. significant cognitive impairment that may preclude certain cognitive behavioural strategies), poor response to non-pharmacological therapies, or limited access to psychological resources may mean that a pharmacological approach to treating anxiety is necessary. The following section outlines currently available evidence-based drug therapy options.

2.12.1 Antidepressant drugs

Various antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have all demonstrated some degree of efficacy in the treatment of anxiety disorders (Baldwin, Anderson and Nutt 2005).

SSRIs (e.g. sertraline, paroxetine, fluoxetine) are the most commonly administered as they have broad spectrum anxiolytic efficacy and are generally well tolerated.(Baldwin, Anderson and Nutt 2005) For these reasons they are generally used as the first line of pharmacological treatment approach for anxiety. Pharmacologically, SSRIs inhibit the post-release reuptake of serotonin by presynaptic nerve terminals, hence increasing the level of available serotonin in the brain (Craig and Stitzel 2003). Drawbacks of SSRIs are that they may cause increased nervousness upon initiation of treatment, insomnia, or nausea. In the

UK NICE recommends offering the SSRI sertraline first as it is the most cost-effective (National Institute for Health & Clinical Excellence 2011).

If SSRIs prove ineffective an SNRI (e.g. venlafaxine, duloxetine) can be offered as the next line of drug treatment. SNRIs work by inhibiting the reuptake of serotonin and epinephrine in the brain, and indirectly increase the level of available dopamine. TCAs (e.g imipramine) and MAOIs (e.g phenelzine) are older generations of antidepressant drugs developed in the 1950s, and for the most part have been replaced by SSRIs. The need to follow dietary restrictions limit the use of MAOIs, and they are generally only used when patients have not responded to, or proved intolerant of, other drug treatment options. Currently NaSSAs (e.g. mirtazapine) are only considered for individuals with post-traumatic stress disorder who prefer not to engage in psychological treatment (National Institute for Clinical Excellence 2005).

Adverse side effects may arise with the use of any intervention. A limited number of studies have examined adverse events in the stroke population but where they have findings have generally been positive for SSRIs. A meta-analysis of 16 placebo-controlled studies including 1320 patients found there was some limited evidence to indicate that SSRIs were associated with decreased risk of death, and also had a relatively low fatal toxicity index (number of poisoning deaths per million prescriptions) (Taylor 2008). Theoretically, the anti-platelet effect of SSRIs would be expected to decrease the risk of thrombo-embolic stroke but could increase the risk of haemorrhagic stroke. Other side effects observed with the use of SSRIs are gastrointestinal and sleep disturbance (Baldwin, Anderson and Nutt 2005). TCAs have been found to be associated with higher risk of cardiovascular adverse events and also been found to be cardiotoxic in overdose (Taylor 2008).

In the general population, SNRIs when compared with placebo are associated with a small increase in diastolic blood pressure, tachycardia, cholesterol, and toxicity compared (Baldwin, Anderson and Nutt 2005; Taylor 2008), hence making them an unlikely candidate for use in stroke survivors. Additionally risk of withdrawal upon discontinuation is greater relative to SSRIs (Baldwin, Anderson and Nutt 2005).

2.12.2 Anxiolytics

Anxiolytics, including benzodiazepines and buspirone have been extensively studied and found to be effective for treating various anxiety disorders. These drugs enhance the effect of the gamma aminobutyric acid (GABA) neurotransmitter which serves to reduce the somatic symptoms associated with anxiety such as muscle tension and insomnia. However the role of these agents as monotherapy is controversial (Canadian Psychiatric Association 2006). Benzodiazepines may be useful for acute anxiety or agitation to help patients in times of acute crises or while waiting for the onset of adequate efficacy of SSRIs, yet there are concerns about possible dependency, sedation, cognitive impairment and other side effects. Caution is advised when using these drugs in elderly patients as they may experience more falls due to psychomotor impairment, or in individuals with a history of substance abuse (Canadian Psychiatric Association 2006).

Buspirone is generally well tolerated. The side effects reported due to its use tend to be mild and may include dizziness, light-headedness, headache, nausea, sweating and nervousness (Canadian Psychiatric Association 2006).

2.12.3 Other drugs

A range of other drugs, including antipsychotics, anticonvulsants, mood stabilisers and hypnotics, may also be used for treating anxiety. Their side-effect burden and the currently limited evidence base for their use means they only have a small role in overall patient management and would generally be restricted for use in patients who have not responded to or proved intolerant of treatments with a more substantial evidence base (e.g. antidepressants).

2.13 Summary

This chapter has provided a review of anxiety and its relevance to stroke, along with the challenges encountered when assessing anxiety in individuals with a chronic illness. It lays the foundation for understanding how these issues may influence the assessment of anxiety prevalence which is discussed in detail in chapter four. The evidence base for treating anxiety after stroke is examined in chapter five in a systematic review of intervention studies. Although research into anxiety after stroke is in its infancy, it is

sufficient to assume that there is a significant influence on outcome post-stroke. The following chapter outlines the common sense model of illness representations and explains its relevance to anxiety after stroke.

3 Chapter Three: Literature Review: Illness Representations

"*After a health threat, a personal and unique representation of illness is formed"*
(Cherrington *et al.* 2004)

3.1 Introduction

The concept of illness refers to the experience of discomfort and suffering (Barondess 1979). Illness differs from disease, in that it is a subjective experience, and is influenced by a host of internal and external factors, such as personal circumstances, personality, stress, culture, and concepts held by the individual about the nature of their disease. Hence unlike disease, which refers to the pathological condition within the body, illness represents a true interaction between the physical and psychological (Bishop 1994). Chapter two introduced the concept of illness schema. The onset of illness can serve as a stressor that activates the emotional vulnerability, defined as schema in cognitive theory (Beck 1985). How an illness (the stressor) is interpreted is important, because according to the principles of cognitive theory, the matching of the input stimuli, with underlying illness schema, could lead to anxiety. Consequently, individuals with the same biological condition, may have large disparities in their experience of illness because they have different underlying illness schema. With this in mind, the interpretation of an illness event may serve as a key determinant in the manifestation of anxiety after stroke.

It has been proposed that the self-regulatory process is one of the best frameworks through which the interpretation, beliefs, adaptation, and behaviours associated with an illness can be understood (Leventhal, Brissette and Leventhal 2003). Various models of self-regulation have been developed (Croyle and Ditto 1990; Skelton and Croyle 1991). However, the Common-Sense Model of illness representation (CSM) has been the most influential and widely accepted model for investigating self-regulation in health (Leventhal, Leventhal and Cameron 2001), and is the one that is focused on in this thesis.

This chapter provides a theoretical overview of self-regulation and the common-sense model, a rationale for its use in stroke populations and a summary of findings to date. This is the last of the literature review chapters and a summary outline of the programme of research in this thesis and how they interrelate is also provided.

3.2 What is self-regulation?

Self-regulation refers to a systematic process involving conscious efforts to modulate thoughts, emotions, and behaviours in order to achieve goals within a changing environment (Zeidner, Boekaerts and Pintrich 2000). It consists of a dynamic system of goal setting, developing and enacting strategies to achieve goals, appraising progress, and revising goals and strategies. Goals, by definition, are future-oriented as they relate to how an individual thinks about their potential and the kind of things they ultimately want to achieve. Feedback loops play an integral role in self-regulation models, in that goals serve as a reference value for evaluating the relative success of efforts (Carver and Scheier 1981). Central to this system is the principle of TOTE (test, operate, test, exit). With TOTE the self-regulatory system will test an input against a standard or reference value. Procedures will then be operationalised to minimise the discrepancy between perception of the present state (the input) and the reference value (goal). The process is repeated until concordance is achieved between the input and reference value, at which point the process is terminated (Miller, Galanter and Pribram 1960).

While TOTE highlights the cognitive aspects of goal setting within the self-regulatory process, emotional responses may also arise. Discrepancy reducing goals (approach goals) aim to diminish differences between input and a reference value. For example, a stroke survivor who was previously healthy may want to return to their pre-stroke level of physical functioning, and become more actively engaged in the rehabilitation process. Discrepancy enlarging goals (avoidance goals) on the other hand aim to increase differences between input and a reference value. These could be thought of as ‘anti-goals’. An example would be a stroke survivor indicating they never want to have another stroke. Within this self-regulatory goal setting process, it has been suggested that the rate of discrepancy reduction or enlargement in tangent with an individuals’ expectations, confidence and sense of positivity or negativity, can play a role in the development of anxiety or depression (Carver and Scheier 1998) (Figure 3-1).

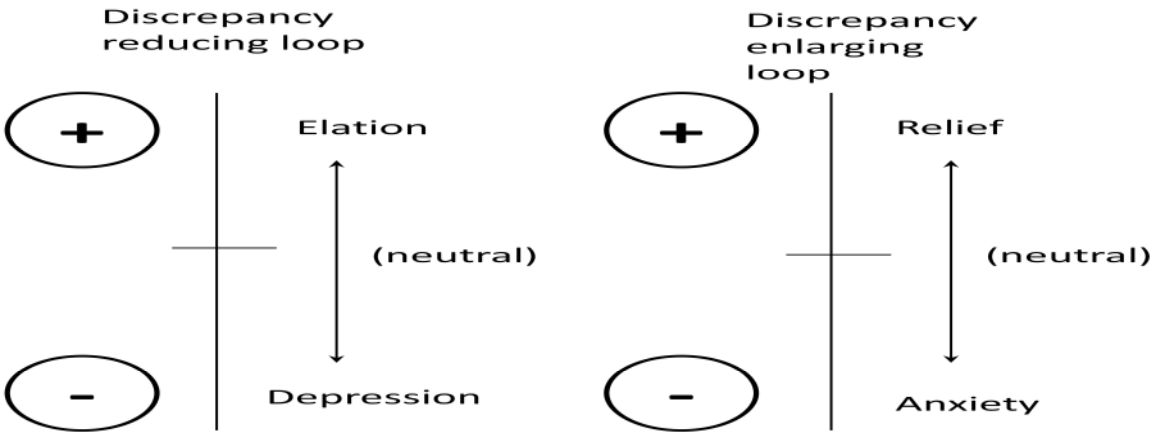


Figure 3-1 Affect generation based on outcome of goal setting

An in-depth account of self-regulation in its entirety as applied to behaviour and outcomes is beyond the scope of this chapter, however the account given above provides an overview of the key features of the self-regulatory process. The description presented in the rest of the chapter and throughout the thesis will be restricted to the common-sense model of self-regulation.

The Common Sense Model (CSM) specifically addresses the self-regulation that occurs during the adjustment and maintenance of behaviours relating to an illness (Leventhal, Nerenz and Steel 1984). Its strength is that it captures both behavioural and emotional processes, and takes into account that these may change over time. Furthermore, the model reflects the ways in which people represent illnesses to themselves.

The CSM hypothesises that individuals are active problem solvers motivated to resolve the threat of illness (Leventhal, Brissette and Leventhal 2003). The "goals" that they are striving towards, are in regards to the somatic experiences, competencies and emotions that are evoked from the biological and psychological self. The strategies and procedures that occur during self-regulation (i.e. health behaviours, emotional regulation) are a result of the interpretation given to the somatic and emotional experiences that arise during illness. In addition to providing a framework for the self-regulatory process, the CSM also provides information about the content of what is being regulated, in that it has identified at least five illness perceptions that coalesce to form illness representations which operates within an individual's pre-existing cognitive illness schema (Leventhal, Brissette and Leventhal 2003). This content which forms an illness

perception or representation, will influence procedures for dealing with the illness threat. While the terms *illness perception* and *illness representation* are often used interchangeably, perception refers to a single belief or cognition about an aspect of the illness (e.g. the symptoms of this illness will not last long), whereas representations refer to mental models which may include other constructs such as perceived vulnerability optimism, and self-efficacy (Weinman *et al.* 1996; Diefenbach and Leventhal 1996).

3.3 Overview of the common-sense model of illness representations

The common-sense model of illness representation (CSM), emerged from a series of studies investigating fear communication intended to influence health behaviour change (Leventhal 1970). These studies showed that high fear messages provoked more fear in individuals, and were more effective in changing attitudes toward a recommended health action than low fear messages. However both the fear and the attitudinal change were transient and generally did not exceed 24 to 48 hours. These studies also found that health actions only occurred when participants exposed to the fear message received a second message that facilitated the development of an action plan (e.g. provision of a health information leaflet). The combination of an action plan and a high or low fear message produced action over a period of days and sometimes weeks, and as subjective feelings of fear and fear induced attitude change faded within 48 hours, it became clear that the actions were linked to some changed way of thinking about or representing the health threat, and not solely the fear of the threat itself. These findings led to the conclusion that individuals create their own common-sense models or representations of their illness in order to make sense of and address their problems. They also realised that the representations influenced subsequent coping responses to deal with the threat (Leventhal, Meyer and Nerenz 1980). Leventhal and colleagues subsequently extended their research to see if their theory would have applicability amongst individuals suffering from real life chronic diseases and conditions (Leventhal, Nerenz and Steel 1984).

3.3.1 Structure and content of the common-sense model

The CSM proposes that incoming stimuli (e.g. a health threat) will result in parallel processing of the phenomena. First is the perceived reality of the health threat (cognitive representations), and the second is the emotional reaction to the threat (emotional

representations) (Figure 3-2). People will act as common-sense scientist when constructing representations of an illness threat, and these representations will generate goals for self-management, and puts forward a process for goal attainment and a criteria for evaluating response efficacy (Leventhal, Brissette and Leventhal 2003).

There are three central tenets underlying this model (Diefenbach and Leventhal 1996). First the individual is an active problem solver both seeking information and acting to test hypotheses about the meaning of their somatic sensations (symptoms) and physical condition and the relevance of these meaning to media and interpersonal messages about health risk. Second, the illness representation is the central cognitive construct that guides coping and the appraisal of action outcomes. Third, the representations are highly individualised and will not necessarily be in agreement with medical facts.

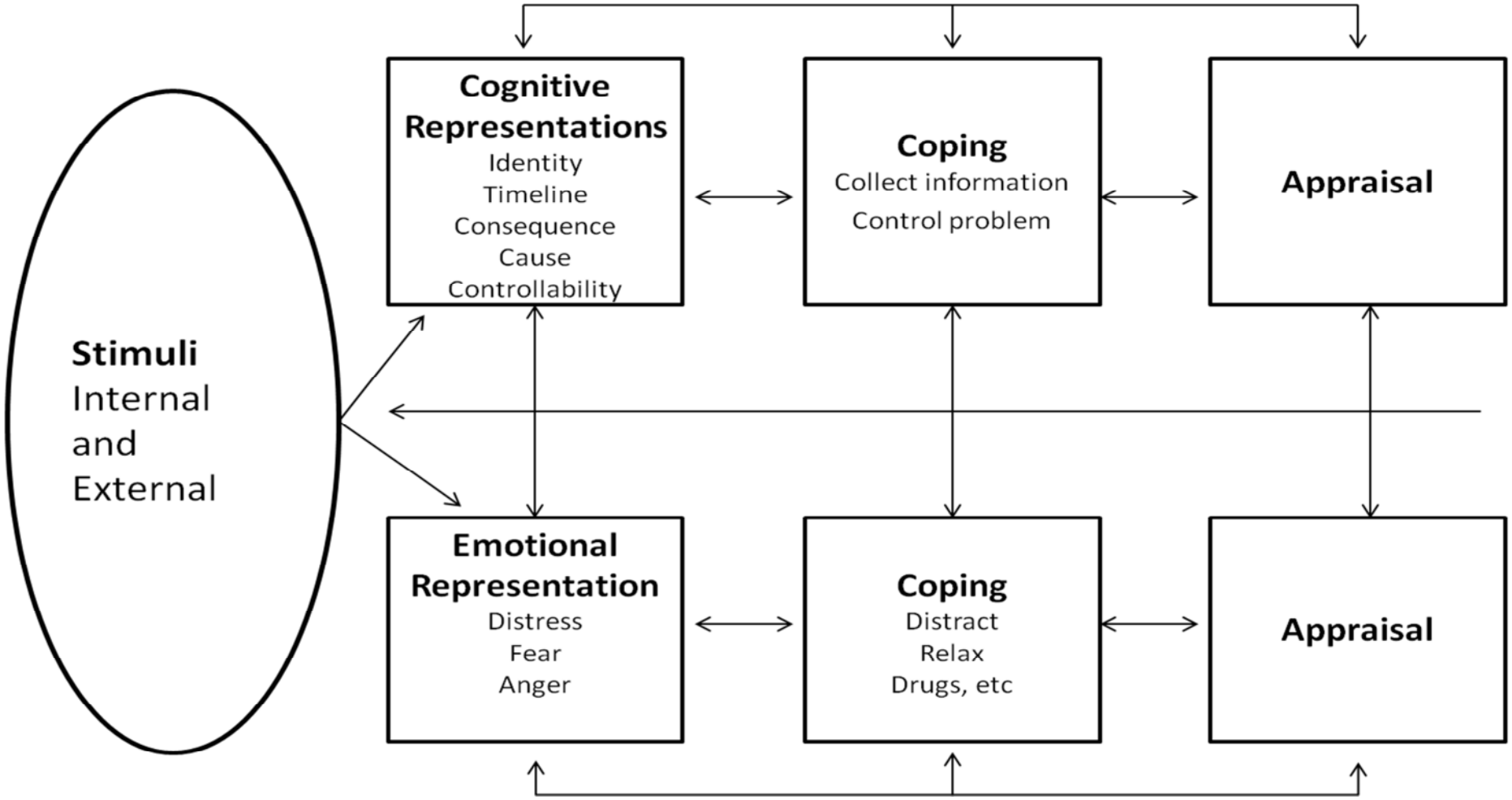


Figure 3-2 The common-sense model of illness representations

On the cognitive level internal and external stimuli will activate pre-existing schema that decode the incoming information based on prior health and illness experience (Diefenbach and Leventhal 1996). How this information is decoded will in turn determine the nature of the illness representations that develop. When the stimulus is an internal, somatic cue, its meaning or representation will depend on its similarity to schematic structures of prior illness episodes or that of a disease they imagine they might have. For example, an individual experiencing numbness or weakness in their arm may interpret this as a sign they are having a stroke because of their knowledge of the F.A.S.T (Face, Arms, Speech, Test) stroke public awareness campaign, which identifies theses as signs of a stroke.

Research has consistently shown that the matching process between incoming stimuli and pre-existing schema will give rise to an individual forming cognitive representations around five distinct domains around their beliefs about the illness: identity, timeline, control, cause, and consequence studies (Diefenbach and Leventhal 1996; Lau, Bernard and Hartmann 1989; Lau and Hartmann 1983). The *identity* domain involves the label or name given to the condition and the symptoms that an individual associates with the condition. People like to have a label for their symptoms, however once a label has been given, they are more apt to interpret diverse symptoms as evidence of the label. For example, individuals diagnosed with hypertension became increasingly more likely to report that their blood pressure was symptomatic the longer they were in treatment, even though hypertension is generally an asymptomatic condition (Meyer, Leventhal and Gutmann 1985). The *timeline* domain connects the stimuli with an expected timeframe. It answers questions such as whether the health condition is acute, chronic or cyclical (e.g. How long will the symptoms of my stroke last? Are stroke symptoms predictable or do they change over time?). Beliefs about timeline will be re-evaluated as time progresses, and it has been suggested that “Inside every chronic patient is an acute patient wondering what happened” (Brown 2002). The *cure/control* dimension addresses beliefs about whether the condition can be kept under control or cured and the degree to which the individual can play a role in achieving this. Essentially it is a measure of empowerment regarding performance of coping behaviours (e.g. “If I take this medicine it will help cure my illness”) or with the efficacy of treatment (e.g. “Taking this medication will be effective in relieving the symptoms of my illness”) (Hagger and Orbell 2003). The *causal* domain refers to views about aetiology,

which may be biological, psychological or environmental. These representations will be based on information obtained from personal experiences as well as the opinions and discourse with significant others, health professionals and media sources, reflecting issues such as stress, environmental pollution, and other pathogens. Beliefs about one's condition may not necessarily be based on medical facts. Finally, the *consequence* domain deals with an individuals' attempts to anticipate the repercussion on various aspects of their life such as their social circumstances, finances or, personal experience.

In parallel with the cognitive representations described, an illness threat will also evoke *emotional* representations, which may include feelings such as distress, fear or anger. Sticking with the F.A.S.T example, feelings of numbness or weakness in an individuals' arms may illicit feelings of fear or panic. Hence both the cognitive recognition of the stroke symptoms and the emotional response would result in the identification of a coping strategy, such as calling an ambulance. If an individual did not make the association between their symptom experience being a sign of a stroke, they could opt for a different coping strategy, such as going for a rest, or even denying the symptoms were present.

Research into the CSM also indicates a pattern of inter-correlations between the five core cognitive domains, which provides evidence for their construct and discriminant validity. In a number of patient groups, inter-correlations between the domains were strong and significant but did not exhibit correlations of a magnitude that was indicative of conceptual overlap (Weinman *et al.* 1996; Moss-Morris *et al.* 2002). Additionally, the correlations showed systematic and logical patterns of association. Illness identity was strongly and negatively associated with the control domain but positively associated with beliefs about serious consequences and chronicity. This would suggest that individuals who viewed their illness as being highly symptomatic (strong illness identity) would also see their condition as chronic, uncontrollable, and having a serious consequence on their life. Analogously, individuals who viewed themselves as having a high degree of control over their condition would view their illness as being less chronic, with fewer serious consequences. However, observed inter-relationships have not always followed a logical trend. In one patient group perceptions of chronicity were inversely associated with seriousness (Heijmans and de Ridder 1998).

3.3.2 Heuristics for validating self-regulation cognitions

The information characterised within each of five domains of the CSM is represented in both abstract (semantic) and concrete (perceptual or experiential) form. From their research, Leventhal and colleagues indentified a number of rules or heuristics involved in converting stimuli into representations (Leventhal, Brissette and Leventhal 2003). They propose that heuristics are used for ongoing interpretation of the stimuli generated by the illness threat, and efforts to control them. This leads to an increasingly elaborate representation of the illness threat over time.

The rule of symmetry refers to the pressure to connect what may be an abstract illness experience with concrete labels. The inverse is also true, in that there is a need to identify symptoms once given a label (illness identity). Evidence of the symmetry rule was provided by a study examining medical compliance of patients with hypertension, and in a laboratory study with individuals who reported more physical symptoms such as headache and tenseness after they were led to believe that their blood-pressure was high (Baumann and Leventhal 1985; Baumann *et al.* 1989). An illness label drove the selective search for "common-sense" symptoms based on underlying illness schema.

The second rule is the stress-illness rule. Stress-illness self-evaluation appears to include an assessment of one's ongoing reaction to environmental events. It involves answering the question "Am I sick or am I stressed?" The attribution of symptoms to a medical condition occurs when no stressful life-event is present, however if a stressful event is present, the attribution moves toward stress and away from illness (Diefenbach and Leventhal 1996). The extent of the shift is moderated by the type of symptoms. Symptoms which are clear signs of disease or injury are not subject to stress attributions. For example, unilateral weakness in limbs or paralysis would likely be seen as more attributed to stroke, as opposed to less descript symptoms such as fatigue or joint stiffness. Two conditions limit the application of the stress-illness rule: the nature of the symptoms; and the duration of the stressor (Leventhal, Brissette and Leventhal 2003). The failure of a symptom thought to be attributable to stress to respond to treatment will raise questions about a benign stress interpretation and activate social communication and care seeking (Mora *et al.* 2002). Individuals have also been found to seek information from close associates in attempts to

validate their personal hypotheses about the nature of their symptoms experience (Zola 1973).

The final rule highlighted in the process of evaluating illness representations is the age-illness rule. It concerns the response to the question "Is this symptom a sign of aging or an indication of illness?" The normal aging process leads to a variety of physical changes, and the distinction between ageing compared with illness related changes becomes more important as one ages. Data showed that care-seeking behaviour was unaffected by age attributions when symptoms were novel and sudden in onset, however symptoms that were familiar and gradual in onset were attributed to age and less likely to promote care seeking (Prohaska *et al.* 1987).

While three rules for validating illness cognitions have been outlined, there are likely other factors that influence the construction of illness representations. For example, testing positive for a condition and perceiving a disease to have a higher prevalence has been shown to be inversely associated with beliefs about its consequences (e.g. the disease is less serious if everybody has it) (Skelton and Croyle 1991).

3.3.3 Factors that influence illness representations

The process involved in developing an illness representation model, mounting a coping response, and experiencing and coping with emotional reactions to the threat do not occur in a vacuum. The model of representation is influenced by a variety of factors, such as personal disposition and cues from social environment.

Individual history can play a significant role in shaping the problem-solving process. Prior illnesses can generate memories which have a major impact on the representation of current somatic stimuli and can also contribute to shaping emotional responses and coping procedures. These memories can operate automatically, creating experiences of dread and powerful emotional reactions without an individual consciously thinking about it (Diefenbach and Leventhal 1996). In addition to illness history, an individual's somatic self provides a backdrop in which symptoms of a new condition are evaluated against. This backdrop is also influenced by biological and genetic factors, and psychological dispositions, although biological and genetic characteristics are likely to influence illness representations

only if they are salient and known to the individual. For example the impact of stroke based on family history could impact the illness representations only after the individual has been made aware of its potential influence (e.g. through the experience of a close friend or family member with a stroke).

Illness representations are also influenced by the social and cultural context. Contrasts in illness beliefs become more apparent when comparative studies are done across cultures. For example a Taiwanese study found that only physical symptoms of depression were described since psychological illness is highly stigmatised in Chinese culture, and individuals within this culture were less able to communicate their emotional states in comparison to individuals from Western cultures (Kleinman 1980). However, this is not a phenomenon that is unique to non-western cultures. One European study found that when patients were depressed they presented to their GP with complaints of physical symptoms (van Rijswijk *et al.* 2009). Feelings of shame and stigma associated with a mental health diagnosis were offered as reasons why individuals tended to deny the psycho-social nature of their symptoms. Such studies show that culture and perceived social acceptability can determine which symptoms are more likely to be reported among those with health conditions. If reporting somatic symptoms is seen as more acceptable than psychological symptoms, the former will be incorporated in the illness representations (e.g. Identity domain) and the latter excluded. Second, the symptomatic focus could establish expectations for treatment. When mental health problems are somatised, patients would expect a somatic treatment and would fail to recognise and respond to treatment for the underlying psychological causes (Diefenbach and Leventhal 1996).

Demographic factors such as age, gender and living arrangements, have also been shown to influence illness perceptions. For example, older individuals are less likely to delay care seeking after symptom onset, as they prefer to resolve uncertainty and worry and are perhaps more cognisant of the frailty of their health (Leventhal *et al.* 1995). Some studies have reported that women tend to report more symptoms associated with their illness than men (Bishop 1994). Additionally, the symptom experience of an illness has been found to be greater for individuals who live alone relative to those who were married or living with others (Pennebaker 1982).

3.4 Coping strategies

Coping with stroke can challenge the stroke survivor's self-concept and contribute to change in personal identity. The CSM model makes an explicit link between illness representation and coping strategies. It proposes they guide the selection of procedures to eliminate or control potential or ongoing threats (Leventhal, Brissette and Leventhal 2003). Coping can take many forms, however two broad categories have been defined: *approach coping* (e.g. going to a doctor, talking to friends about emotions); and *avoidance coping* (e.g denial, wishful thinking) (Ogden 2000).

An extensive review of coping strategies, models and procedures is beyond the scope of this chapter, however Ogden (2000) highlighted three approaches to coping that were relevant in her review of illness representation: coping with a diagnosis (Shontz 1975); coping with the crisis of illness (Moos and Schaefer 1984); and adjustment to physical illness and theory of cognitive adaptation (Taylor 1983).

Shontz (1975) proposed that individuals will go through a state of shock upon receiving a diagnosis of a chronic disease. After this they will have an encounter reaction that is characterised by disorganised thinking and feelings of loss, grief, helplessness and despair. The final stage of in this model of coping was identified as retreat, at which point the individual would deny the problem and its implications and retreat into the self. Shontz proposed that once in the retreat stage, the individual could gradually deal with the reality of their diagnosis.

In the illness as crisis model (Moos and Schaefer 1984) three phases of the coping process were identified. The first phase consisted of cognitive appraisal whereby an individual appraises the seriousness and significance of the stimuli. The appraisal will be influenced by various factors such as knowledge, previous experience and social support. Following the cognitive appraisal adaptive tasks are used as part of the coping process. These tasks will be general (e.g. preserving a reasonable emotional balance after being diagnosed with a serious condition) and illness related (e.g. dealing with symptoms experienced). Following the used of adaptive tasks, it is proposed that the individual will adopt one of three coping skills. Appraisal focused coping involves attempts to understand the illness and represents a search for meaning. Problem focused coping consists of

confronting the problem and reconstructing it as manageable. The last strategy is emotion focused coping whereby the individual seeks to manage emotions, and maintain emotional equilibrium.

The final model of coping that will be described in this section is the adjustment to physical illness and theory of cognitive adaptation (Taylor 1983). It suggests that coping with a threatening illness consists of three processes: a search for meaning (e.g. knowing what caused the illness), a search for mastery (believing the illness is controllable), and a process of self-enhancement (feeling they are better off than other people with the illness). Taylor (1983) argued that these three processes are central for developing and maintaining illusions and that these illusions should be considered a process of cognitive adaptation. In this model the individual is seen as self-regulatory and as motivated to maintain the status quo.

Although the CSM proposes a direct link between illness representations and coping, findings in the literature are mixed. A systematic review that identified and classified categories of coping behaviours and strategies examined in illness representation research, showed identity and consequence constructs were significantly and positively related with avoidance/denial, and expressing emotions (Hagger and Orbell 2003). On the other hand, the control/cure domain was not associated with avoidance/ denial or expressing emotions, but was significantly associated with problem-focused coping, and cognitive reappraisal. However 14 of the 28 relationships identified between illness representation dimensions and coping strategies were non-significant.

Although these findings call into question the relationships outlined in the CSM, it has been argued that the lack of consistent associations between cognitive representations and coping behaviours may be more of a function of the inadequacy of measures used to assess coping rather than a misspecification of the CSM itself (Hagger and Orbell 2003). The coping measures used in the studies examined were criticised for their excessive generality and failure to account for individual differences in coping styles, goals, and perceptions of success.

3.4.1 Coping and stroke

A few studies have assessed coping strategies and their affect on outcomes in stroke survivors. A qualitative study looked at the meaning stroke survivors gave to their stroke (appraisal) and coping strategies (Rochette *et al.* 2006). It found that seven appraisal themes (unpredictability, feeling overwhelmed, feeling out of control, threat, turning point, acceptance/resignation and future prospects), and five coping themes (active and passive compensation, escape, change in how the situation is perceived, and the use of resources) emerged during the process of adapting to stroke. They concluded that the fear of another stroke served as a source of motivation for adopting active coping strategies.

In another qualitative study, stroke survivors described coping strategies that centred around social support, active behavioural strategies, and cognitive strategies (Ch'ng, French and McLean 2008). Positive re-interpretation, and acceptance of their stroke were cited as coping strategies that helped these individuals feel better. Coping using positive reinterpretation has been associated with more positive mood after stroke (Boynton De Sepulveda and Chang 1994). On the other hand avoidant coping such as denial, has been linked to depression in stroke survivors (King *et al.* 2002). Relaxation, use of humour, and comfort gained from religious beliefs are other cognitive coping strategies found to be helpful for stroke survivors (Ch'ng, French and McLean 2008).

3.5 Rationale for investigating illness representations in stroke survivors

Illness represents a fundamental threat to survival and well being, with few life events more capable of eliciting anxiety and fear. When an individual has a stroke, they are likely to develop a pattern of beliefs about their condition, or they may already have pre-existing ones. For example, a study in hospitalised patients found that the majority believed that having a stroke (even a minor one) was tantamount to, or worse than death (Hanger *et al.* 2000). Such views could be key determinants of behaviour directed at managing illness (e.g. willingness to engage in rehabilitation), and could also have an influence on other health outcomes such as mental health status or quality of life.

Despite their importance, an individual's views of their illness or symptoms are rarely sought in medical interviews or in interactions with other health professionals (Petrie and

Weinman 2006). The components of the CSM have been outlined above, yet the fascinating aspect of this concept is the diversity that can be observed within the same patient group, and these representations could lead patients with similar medical conditions along very different trajectories. On the other hand, illness representations are also dynamic in nature, and are amenable to change in response to shifts in patient progress, environment, and personal circumstances. A study carried out in patients with cardiovascular disease found that a cognitive-behavioural intervention individualised to alter their perceptions about their disease was effective in producing positive changes in the patients views of their condition (Petrie *et al.* 2002). They also found that the intervention resulted in patients feeling better prepared for leaving hospital, and were more likely to return to work.

At its core the CSM seeks to ask the basic question "Does it matter what patients think?" Examining illness representations is valuable for both furthering understanding of illness-related coping, and gaining insight into their influence on health related outcomes such as anxiety or depression. From a practical perspective, knowledge of illness representations in stroke survivors could prove useful for informing the stepped care approach for managing psychological distress. Additionally, an understanding of illness representations also has the potential to contribute to the management of other health related outcomes that arise due to stroke, such as physical recovery, social relationships, or quality of life if any associations are observed

3.6 Assessing Illness Representations

In their original work, Leventhal and colleagues often used in-depth, semi structured interviews that focused on the individuals' concrete illness experiences in order to elicit their representations. While this approach was very valuable, it was also very time consuming, produced large variations in the quantity and quality of information, and it was impossible to generalise data from these qualitative interviews beyond the study sample.

Individuals are rarely asked about their illness representations in clinical settings but would usually be happy to discuss their ideas if the invitation is welcoming and they do not feel they are being tested on their knowledge (Petrie and Weinman 2006). Some suggestions for possible opening questions are "Many patients develop their own ideas about their illness and I would be interested in discussing these with you", which could be

followed up with specific questions such as “What are the main consequences of this illness for you?”

In response to the drawbacks of informal assessment, the illness perception questionnaire (IPQ) and its subsequent revised version (IPQ-R) were developed (Weinman *et al.* 1996) (Moss-Morris *et al.* 2002). They provide a straightforward assessment of the major components of illness representations and can be tailored to specific illnesses or medical conditions without losing psychometric validity. The IPQ-R has been used across a range of illnesses (Hagger and Orbell 2003). This questionnaire is discussed in detail in chapter six. It should be mentioned that some criticism has been levelled at the use of quantitative scales, as their reporting tends to provide descriptive accounts of the different illness domains in isolation of each other (Clatworthy *et al.* 2007). This has resulted in moving away from obtaining rich idiographic accounts of illness representation, towards a nomothetic scientific approach.

A more recent and different approach to assessing illness representations is the use of patient drawings (Petrie, Jago and Devcich 2007). Thus far drawings have been used in illnesses where individuals can easily visualise their pathology. A study in patients with myocardial infarction found that the size of damage drawn by patients on their heart was associated with a slower return to work and more negative representations of their condition, and was a better predictor of these outcomes than biological markers of the heart condition (Broadbent *et al.* 2004). Three month longitudinal follow-up of this patient cohort found that an increase in the size of the heart damage drawn was an indicator of poorer recovery in terms of increased heart focused anxiety, complaints of ill health, worry about having another myocardial infarction, and higher use of healthcare. Once valid methods for assessing drawing are developed, their use in determining illness representations could have applications for stroke, especially for individuals with communication deficits.

3.7 Illness representations and chronic illness

Taking into account the role of the CSM is relatively novel concept within stroke research and the body of evidence is still in its infancy. However comprehensive work has been carried out in numerous other groups with long-term conditions (Kaptein *et al.* 2003;

Scharloo and Kaptein 1997). A selective review of over 30 studies examining illness representations found that different illness representations emerged as important correlates or predictors of outcomes in different chronic diseases. The illnesses examined were, asthma, chronic obstructive pulmonary disease, neurological diseases (these included Huntington and Alzheimer disease, traumatic brain injury, and multiple sclerosis), cancer, and cardiovascular disease (Kaptein *et al.* 2003). Findings from neurological studies found that identity and timeline representations were associated with depression and poorer functional status. Alternatively, in cardiovascular disease cure/control beliefs were strongly correlated with cardiac rehabilitation attendance. Strong illness identity was associated with greater sexual dysfunction, and a belief about serious consequences was related to decrease in recreational and social activities. Additionally older patients also perceived less control over their disease.

3.8 Illness representation and stroke

A search of Medline (1951-August 2012), EMBASE (1947-August 2012), AMED (1985-August 2012), PsycINFO (1806 – August 2012), and CINAHL (1960- August 2012) combining various terms for illness representation and stroke found five studies using a structured questionnaire to examine the relationships between illness representation and outcomes in the stroke population. The results from the search are summarised in Table 3-1. Four studies (Twiddy, House and Jones 2012; Dinsmore *et al.* 2010; Ford 2007; MacLeod, Abdullah and Wilkinson 2010) were based on the CSM and used the illness perception questionnaire, while the other (Johnston *et al.* 1999; Morrison, Johnston and Mac Walter 2000) examined the role of control beliefs using the Recovery Locus of Control (RLOC) scale (Partridge and Johnston 1989). The RLOC measures the role of control cognitions in recovery, which differentiates between having an internal locus of control (e.g. believing circumstances are controlled by ones personal behaviour) or an external locus control (e.g. believing circumstances are controlled by external forces or chance).

Two of the studies (Dinsmore *et al.* 2010; MacLeod, Abdullah and Wilkinson 2010) using the CSM were reported only as conference abstracts and are summarised in Table 3-1. Another study (Ford 2007) was a cross-sectional unpublished doctoral thesis study with the primary aim of investigating the association between illness representations and depression

in first-time stroke patients. Forty patients were recruited in the early stages post stroke (2-6 weeks), and significant bivariate correlations between illness identity, chronicity, consequence and emotional representations with depression were reported. This study also found that believing a stroke would have a substantial consequence on ones life was significantly associated with increased anxiety. As patients were recruited shortly after stroke, this study was able to uncover early understandings of the event. Limitations of this study are its small sample size which could result in biased and unstable estimates, and its cross-sectional design means that causal relationships could not be determined. The final study (Twiddy, House and Jones 2012) carried out a longitudinal assessment in patient and carer dyads and assessed various relationships between individual and interpersonal illness representations about stroke and patient levels of distress. These findings suggest that negative illness representations of both patients and carers were associated with distress. This was the first study to examine the impact that carers beliefs may have on stroke patients, and the longitudinal design allowed for predictive relationships to be examined. However the small sample size meant that several independent analyses had to be conducted, and all illness representations could not be included in one model.

In the study using the recovery locus of control, physical recovery, depression and anxiety were predicted over time (Johnston *et al.* 1999; Morrison, Johnston and Mac Walter 2000). At one-month post stroke, they found that control beliefs were significantly associated with both anxiety and depression. However six months later, after controlling for baseline levels of anxiety, perceived control was not a significant predictor of distress. It is unclear whether the perceived control reference group was internal or external, and this study suffered from large losses to follow-up so result findings may be biased.

In summary these studies seem to indicate there is some association between illness representation and mental health conditions in stroke survivors. However the focus has rarely been on anxiety, even in studies that have used assessment tools where it is measured. Two of the studies were available as conference abstracts only, so the full findings could not be explored. Additionally, few studies employed a longitudinal design, and where they have the sample size has been small, meaning that causal relationships between illness representations could not be adequately investigated. The larger study that

had a longitudinal design used an alternative framework for assessing illness beliefs to assess the relationships with anxiety after stroke.

Table 3-1 Summary of studies investigating illness representation in stroke populations

Author, Location	Aim	Sample	Methods	Measures	Findings
(Dinsmore *et al.* 2010) Conference abstract Ireland	To examine the quality of life and illness perceptions in stroke patients at two different health centres	N=203 Recruited will in hospital	Longitudinal with baseline and 12 month follow-up post-stroke	IPQ-R, SEIQoL-DW, HADS, SSQOL, SISE, RLOC, MSPSS	Positive illness perception was important in determining increased QoL, positive internal locus of control and self-esteem increased QoL and an increase in perceived social support and decreased anxiety and depression increased QoL
(Ford 2007) UK [unpublished thesis]	To investigate the association between illness perceptions and depression after stroke	N=40 73 yrs (mean age) 58% female 98% White Recruited 2-6 weeks post-stroke	Cross-sectional survey	IPQ-R, HADS, MMSE	Depression Significant association with Illness identity (r_s=.32), Chronic timeline (r_s=.45), Consequences (r_s= .55), and emotional (r_s= .40) representations After adjustment for clinical and demographic factors only consequence representations significant predictors of depression (β=.427, p=.002) Anxiety Significantly associated with consequence (r_s= .39) representations
(Johnston *et al.* 1999; Morrison, Johnston and Mac Walter 2000) UK	To investigate if illness cognitions predicted recovery from stroke, depression, and anxiety, and to determine if association was mediated by exercise as a coping response	N=71 Recruited within 3 weeks post stroke Mean age 69 yrs 51% male	Longitudinal survey with follow-up at 1 & 6 month post-discharge	RLOC, Exercise coping scale, HADS, Barthel Index	Control cognitions significantly associated with anxiety ((r=-.47, p<.001) and depression (r-.43, p<.001) 1 month post stroke In a multiple regression analysis, perceived control was not a significant predictor of anxiety or depression at six months, after controlling for anxiety and depression at 1 month
(MacLeod,	To assess patients perception	N=120 with TIA or	Cross-	Brief-IPQ,	Median scores for*:

Author, Location	Aim	Sample	Methods	Measures	Findings
Abdullah and Wilkinson 2010) European Stroke Conference Abstract UK	of the significance of TIA and their beliefs and attitudes to secondary prevention interventions	minor stroke (modified Rankin Scale score 0-1)	sectional survey	Beliefs about Medicines Questionnaire, Adherence to secondary prevention medications	-perceived consequence (mean 4.88, SD=2.67), -emotional representation (mean 4.9, SD=3.4), -personal control (mean 4.0, SD=3.2) Stronger beliefs for: -treatment control (mean 7.7, SD=2.1) * scores range from 0-10 Concluded that patients do not regard TIA as having important implications for their future health and feel they do not have personal control over the condition. Many only seek medical advice as a result of external pressure.
(Twiddy, House and Jones 2012) UK	To determine if patient and carer distress were associated with illness representations	N=42 stroke patient and partner dyads Recruited within 2 months post stroke Mean age 65 yrs (patients)	Longitudinal survey with baseline and 3 month follow-up	IPQ-R, GHQ-28, Barthel Index, Significant Others Scale	*Baseline:* Patient coherence inversely associated with their distress score (β=-3.38, p=.04), however carer coherence significantly predict patient distress (β=2.61, p=.05) *Three month follow-up:* Higher patient illness identity (β=.73, p=.02), consequence (β=8.37, p<.001), emotional (β=6.69, p=.01), and psychological cause (β=3.69, p=.02) at follow-up were significant predictors of distress at follow-up. Discrepancy was also a significant predictor of distress at follow-up (β=-7.73, p=.04)

GHQ-28: General Health Questionnaire (28 items), HADS: Hospital Anxiety and Depression Scale, IPQ-R: Illness Perception Questionnaire- revised version, MMSE: Mini-Mental State Examination, MSPSS: Multiple Perceived Social Support Scale, QoL: Quality of Life, RLOC: Recovery of Locus of Control, SEIQoL-DW: Schedule for the Evaluation of Individual Quality of Life Direct Weighting, SISE: Single Item Self-Esteem, SSQOL: Stroke Specific Quality of Life Scale

3.9 Critique of the Common-Sense Model

The explosion of research using the common-sense model indicates a keeness to determine how illness representations may influence both coping and outcomes in a diverse range of chronic disease (Hagger and Orbell 2003). However some limitations of the model have been observed. The premise that illness representations influence coping, and that coping is related to outcomes (i.e. coping model as required mediator) has been challenged. Research currently seems to indicate that illness representations may be associated with outcomes (e.g. mental health, health behaviour) independently of coping (Hagger and Orbell 2003). However some have argued that the lack of success in testing the impact of coping could have more to do with the available coping measures which some say assess coping styles, rather than specific actions and procedures as is intended in the CSM.

Another criticism is the current quantitative direction that research into illness representations has taken. As outlined in section 3.6 several quantitative tools have been developed in an attempt to make research in the field generalisable beyond the specific participants involved. While such a move was needed to test concepts empirically, this has shifted from the original intent of garnering a common-sense understanding of the personal health beliefs held by an individual. Cluster analysis has been proposed as a method to help establish a middle-ground between the qualitative and quantitative approaches to investigating illness representations (Clatworthy *et al.* 2007). Rather than looking at individual illness schema, cluster analysis enables the identification of groups of individuals who share similar beliefs, and the utility of the SRM in predicting outcome from these beliefs can still be tested.

It is highly probable that various factors influence the pathway from representation to outcome. However the SRM does not make specific predictions about the role of the interaction with other variables. This consideration is vital especially when carrying out research in samples drawn from established disease populations, such as attendants at hospital out-patient clinics (e.g. stroke patients going for follow-up appointments), as they are likely to be exposed to material designed to affect their disease knowledge or coping strategies. In the case of stroke survivors they are usually provided with information brochures from the Stroke Association or may be asked about how they are dealing with any

effects of the stroke by their GP or stroke consultant. This leads to another weakness of the CSM, in that much of the research has been carried out in non-stroke populations. Stroke is different from many other diseases in that it is an acute event, with the potential to have long-term consequences in all domains of physical, social, and mental functioning. Subsequently, the representations observed in the stroke population may differ from those observed in other illness groups.

3.10 Summary

- The common-sense model of illness representations is a framework which seeks to identify the cognitive beliefs and emotional interpretations that influence health behaviour and outcomes
- Representations around illness centre around five core cognitive domains:(Identity, Timeline, Control/cure, Cause, and Consequence
- An individual will draw on a series of rules for validating their representation model
- Representations are influenced by a range of internal and external factors
- The CSM proposes a direct link between coping strategy, and between coping strategy and health behaviour or outcome, however this relationship has not always been supported in the research literature
- Illness representations have been found to be associated with a range of outcomes in several groups with long-term conditions, however evidence is scant in stroke

3.11 Overview of research questions addressed in the thesis

The first three chapters have sought to highlight the detrimental impact of stroke with a focus on the psychological consequences of anxiety in particular. The concept of illness representations was introduced, and an outline of their influence on health behaviours, and outcomes such as mental health distress established. The literature review chapters highlighted that published work regarding anxiety and stroke was scant. As a first step, it was decided that it was a priority to establish the extent to which anxiety after stroke was a problem, and to identify literature that addressed how anxiety after stroke could be treated. The last phase of this research programme grew out of an interest in understanding whether health beliefs were associated with anxiety after stroke. Three separate but associated studies were carried out to answer relevant questions. The following sections

provide a brief overview of the work that will be presented throughout the rest of the thesis. Specific details about design and methodology and findings are included in following chapters.

3.11.1 Study 1: What is the prevalence of anxiety after stroke?

A systematic review of observational studies was conducted to estimate the prevalence of anxiety after stroke. At the time of commencing the PhD no such work had been conducted. This review is discussed in detail in chapter four.

3.11.2 Study 2: What interventions are effective in treating anxiety after stroke?

A Cochrane systematic review of randomised clinical trials was carried out to identify high quality studies of interventions used to treat anxiety after stroke. This review is discussed in detail in chapter five.

3.11.3 Study 3: Are illness representations associated with anxiety after stroke?

This was an empirical study that sought to identify whether illness representations were associated with anxiety after stroke. A cross-sectional baseline analysis and a longitudinal follow-up analysis were conducted. The specific questions under investigation in this study were:

1. Are there any differences in illness representations between anxious and non-anxious stroke survivors at baseline?
2. Are illness representations at baseline associated with anxiety levels at baseline?
3. Does the prevalence of anxiety, and anxiety symptom severity in stroke survivors change over time?
4. Do stroke survivors change their illness representations over time?
5. Do illness representations predict anxiety level at follow-up in stroke survivors?

The methods for the empirical study are described in chapter six, and the results in chapters seven and eight. The final chapter discusses the limitations of the empirical study, along with clinical and research implications for the future.

4 Chapter Four: Study 1- Frequency of anxiety after stroke: A Systematic Review and Meta-analysis of Observational Studies

4.1 Introduction

This systematic review was the first of three studies in the programme of research encompassed in this thesis. It sought to quantify the prevalence of anxiety after stroke based on findings in the research literature and collate information about correlates of anxiety after stroke. A comparative narrative account with a high quality systematic review of depression after stroke is provided and research gaps highlighted. The overall findings are summarised and recommendations for future work considered.

4.2 Rationale for review

Anxiety can have severe consequences on the course of physical recovery, and quality of life post stroke (Schultz *et al.* 1997; Ahlsio *et al.* 1984). Previous estimates of the frequency of post-stroke anxiety ranged from 1 to 65% (House *et al.* 1991; Macniven *et al.* 2005). Even though there was a lack of consistency in the findings, anxiety after neurological disease and especially stroke remained a relatively neglected topic (Kanner and Barry 2003; Annoni *et al.* 2006). Despite this, clinicians and patients continued to report anecdotally they believed it to be an under-recognised concern. There was much uncertainty regarding the extent to which anxiety after stroke was a problem, however previous attempts to synthesise the phenomenon have taken a narrative rather than a systematic approach (Ferro, Caeiro and Santos 2009).

Systematic reviews are considered to be the highest level of evidence within the research framework, and are the best way to synthesise the information that is available for a specific topic (Evans 2003). They differ from the traditional literature or narrative reviews in that they are led by a protocol developed prior to the commencement of research, and adhere to rigorous standards and processes that result in the work being replicable. A well conducted systematic review will address some of the issues with reporting biases that are present in non-systematic methods of reviewing evidence. Systematic reviews are undertaken when there are substantive questions, and primary studies appear to yield

disparate results (Hemingway and Brereton 2009). Given the contrast in findings regarding the prevalence of anxiety after stroke, it was important to undertake research that had the potential to yield a unbiased, and impartial summary of the existing research evidence on its occurrence. It was also recognised that such a review had the potential to enhance the profile of anxiety within the wider context of stroke research.

4.3 Aim of review

The primary aim of this review was to summarise all available information regarding the prevalence of anxiety disorders, and anxiety symptom "caseness" as derived from scores on anxiety scales, after stroke. Whether estimates varied based on the diagnostic or screening tool used, or select study quality criteria indices were also investigated. A secondary aim was to collate and describe information about the correlates of anxiety reported in the studies included in the review.

4.4 Methods

This review was guided by the following principles of systematic reviewing (Khan *et al.* 2003). These include: framing the question, identifying relevant work, assessing quality, summarising the evidence, and interpreting the findings.

4.4.1 Inclusion/ Exclusion Criteria

The review included data from observational studies published in journal articles, abstracts, and conference proceedings involving populations or groups of patients who had a clinical diagnosis of ischemic or haemorrhagic stroke or transient ischemic attack (TIA), and were diagnosed with an anxiety disorder, or assessed for anxiety symptoms on a rating scale such as the Hospital Anxiety and Depression Scale (HADS). Studies were excluded if they:

1. were intervention studies because the participant eligibility requirements for clinical trials tends to result in a very select subset of the general stroke population being included. The prevalence of anxiety estimated in this group could be significantly higher or lower than would be expected if a less biased method of case ascertainment were used;

2. were limited to patients with subarachnoid haemorrhage as these individuals have a substantially different management strategy from individuals with ischaemic stroke;
3. used a non-specific measure of psychological distress not designed to screen for anxiety, as these are not appropriate for establishing anxiety and could be estimating other forms of mental health distress, such as depression or suicidality;
4. involved retrospective recruitment or reporting of mood because this could result in participant recall bias (Raphael 1987);
5. used a convenience sample as this form of sampling only allows individuals who are available and known to the researcher to be included and is considered to be an extremely biased method of sampling (Freedman *et al.* 2009) ;
6. reported anxiety as a continuous outcome without providing categorical assessment as it is not possible to obtain the proportion of individuals with anxiety when it is reported in this way; or
7. measured anxiety by proxy, as a third party's perception of anxiety could be different to that of the stroke survivor.

Non-English language papers that were potentially eligible based on their title or abstract were translated, and were included in the review if deemed to have met the eligibility criteria.

4.4.2 Study identification, data extraction and quality appraisal

Electronic searches in MEDLINE, EMBASE, PsycINFO, Allied and Complementary Medicine, CINAHL, and Proquest dissertation databases were conducted using the terms "stroke" or "cerebrovascular disorders" or "cerebrovascular accident" in combination with "anxiety disorders", or "adjustment disorders", or "neurotic disorders", or "mental disorders", or "worry", or "fear". Search terms were combined with the "explode" feature and no language restrictions were put in place (see Appendix A for detailed search strategy). One reviewer (ACB) developed and conducted the initial search from database inception to

March, 2010 and later updated it up to March, 2011. Reference lists from included studies were checked for other studies that may not have been found in the database search.

One reviewer (ACB) screened and identified studies against the selection criteria, and a second reviewer (PK) conducted a random check of approximately 10% of titles and abstracts to assess the reliability of initial screening. Independent data extraction by ACB and PK was performed for all eligible studies. Information about study design, setting, and patient characteristics was recorded. When relevant data was missing (e.g. the study used a rating scale that measured anxiety but did not report findings in the publication) study authors were contacted in order to obtain the pertinent information.

A number of consensus statements have been published to encourage high quality reporting in empirical research, which include the Quality Reporting of Meta-Analyses of Randomised Controlled Trials (QUOROM) (Moher *et al.* 2000), the Meta-Analysis of Observational Studies (MOOSE) (Stroup *et al.* 2000), and the Strengthening Reporting in Observational Studies (STROBE) (von Elm *et al.* 2007) statements. These statements were primarily designed to assist study authors when writing up findings from their studies, rather than individuals looking to assess the validity of what they were reading. Another issue is that some of these statements have produced checklists that are quite lengthy, making their use challenging when trying to synthesise large volumes of information. Study quality was assessed using a modified version of the Quality Assessment Tool for Systematic Reviews of Observational studies (QATSO)(Wong, Cheung and Hart 2008). This is a short, easy to use checklist that attempts to strike a balance between the number of inter-study items that are assessed, but is still simple and practical to use. Hence, while the ability to provide comparisons on a range of study items is lost, it does address the issue of non-use of quality appraisal tools that has been observed in systematic reviews of observational studies (Mallen, Peat and Croft 2006). Each study was evaluated based on their method of participant recruitment, instrument used to measure anxiety, proportion of eligible patients who participated, proportion lost to follow-up (if applicable), and adequacy of descriptive details about the study populations. Table 4-1 shows the indices used to assess the quality of the observational studies included in this review.

4.4.3 Data synthesis

Studies were grouped into four categories based on method of case ascertainment. These were categorised as: P*opulation-based studies,* which attempted to recruit all stroke survivors in a particular geographical area over a given period of time. These studies were regarded as the least biased method for identify cases in cohort studies; *Hospital-* and *rehabilitation-based studies* recruited in-patients, or those attending rehabilitation facilities. Lastly *community-based studies* recruited patients not in hospital or rehabilitation facilities, with no attempt to include all stroke cases in the geographical area (e.g. only patients from select general practices were included). Studies were also stratified by three time periods: the "acute phase" (defined as less than one month post-stroke), "mid-term phase" (one to five months post-stroke), and "long-term phase" (six or more months post-stroke).

Table 4-1 Indicators used to assess study quality

Criteria	Question asked to assess criteria	Possible score
Was the recruitment of Stroke Patients biased?	Criteria for enrolment was obtained patients enrolled in a pre-defined consecutive manner (e.g. consecutively admitted hospital or rehab patients, randomly selected patients from a GP's register) Probability sampling used (for example simple random, systematic, stratified random, cluster, or two-stage and multi-stage sampling, population study)	Yes No
Was the measurement of anxiety objective? (Internal Validity)	Clinical interview administered with DSM or ICD diagnosis of anxiety Validated anxiety measure (e.g HADS, Beck Anxiety Inventory, GHQ 30, 28 and 12. Wimbledon Self-Report Scale) Non-validated anxiety screening measure (e.g. single question, self-report)	Yes Possible Uncertain
Did the Study report a response rate and/ or number lost to follow-up?	Response rate and/or loss to follow-up reported Response rate and/or loss to follow-up NOT reported	Yes No
Was the Response rate greater than or equal to >60% AND/OR the loss to follow-up less than or equal to 40%?	Response rate (≥ 60%) and/or loss to follow-up (≤ 40%) Response rate (<60%) and/or loss to follow-up (>40%) Insufficient information provided to determine response rate and/or lost to follow-up	Yes No Unclear
Sufficient core data elements included to describe the population (Core elements are Age, Gender, and Level of Disability)? (External Validity)	The proportions for at least two core data elements included in the population description: *(Gender, Age distribution, physical disablity) Other elements such as Stroke subtype, Marital status, Cognitive capacity, Employment status, Physical functioning may also be included)* Less than two core data elements of patient characteristics are included in the population description:	Yes No
Funding body for the study may have biased the results that are reported?	Potential for reporting bias exists based on source of funding No obvious potential for biased results based on source of funding	Yes No
Author declared conflict of interest may have biased the results that are reported?	No obvious potential for conflict of interest Conflict of interest could bias results that were reported	Yes No

4.4.4 Meta-Analyses

Meta-analyses were conducted to estimate a pooled estimate of the prevalence of anxiety after stroke. Meta-analyses provide a quantitative approximation of the phenomenon under investigation, and are based on combining "pooling" the information obtained from studies included in the systematic review. There are different philosophical principles that underlie meta-analyses, which have resulted in two methods of analyses. The respective methods are known as fixed effects and random effects model.

The fixed effect method of analysis is based on a mathematical assumption that there is an underlying "fixed" or overall rate and that every study is trying to estimate this rate (Borenstein *et al.* 2010). Under this assumption, if every study were infinitely large, each would yield an identical result. This is the same as assuming there is no statistical heterogeneity among the studies. Fixed effect models give more weight to larger studies with smaller standard error. Some have argued against the fixed-effect model because it is implausible that the studies collected in a systematic review could represent the actual sample of infinitely large pool of all possible studies that could ever be done (Bonett 2009).

The random effects method proposes that there is a distribution of true prevalence and the aim is to estimate the mean of this distribution (Borenstein *et al.* 2010). The random effects method gives a more equal weighting to all studies in that larger studies lose influence while small studies gain influence, and study weights are based on within-study and between-study variance. The confidence interval for the summary measure tends to be wider than the fixed effect model unless there is no between-study variance, in which case the fixed effect and random effects model will yield the same result. The random effects model was used in this study because its underlying assumptions were more likely to fit the actual sampling distribution, it did not impose a restriction of assuming a common prevalence, and it allowed for conclusions to be generalised beyond the sample of studies included in the review. The meta-analyses findings are displayed graphically in a forest plot.

The concept of heterogeneity was introduced when describing the fixed and random effects models. Heterogeneity refers to the variability observed when bringing studies together. This can occur due to clinical diversity (e.g. differences in participants or different methods of assessing the outcome of interest), or methodological diversity (e.g. differences

in study design). Heterogeneity is measured statistically with the chi-square (X^2) test. Chi-square assesses the likelihood that the observed differences between the studies is due to chance. A low p-value (or a large chi-squared statistic relative to its degree of freedom) provides evidence of heterogeneity. In combination with the chi-square test, the I-square (I^2) statistic provides an estimate of the percentage of the observed differences between the studies which is not due to chance. Possible I-square values range between 0% and 100%, and it is considered substantial when values are greater than 50% (DerSimonian and Laird 1986).

Given the potential for a variety of factors (both those identified a priori, and those that remain unknown) to contribute to the heterogeneity of the findings,

Several meta-analyses were conducted that stratified studies along the following characteristics:

1. anxiety disorder diagnosis vs. anxiety symptoms as assessed by a rating scale, in order to evaluate if symptom screening resulted in differential estimates of prevalence;
2. source of study population (i.e. population, hospital, rehabilitation, or community), as it was thought that clinical cohorts could have different rates of anxiety as opposed to population samples that include well and unwell individuals;
3. an interaction between source of study population and time post-stroke, in order to compare this review with a systematic review of the prevalence of depression after stroke;
4. First stroke vs. recurrent stroke, as having a previous stroke could result in the event being seen as more (or less) anxiety provoking given the individual would have some familiarity with having a previous stroke;
5. the proportion of eligible individuals that participated in the study, as studies with greater lost to follow-up could be providing different prevalence estimates.

Studies using the DSM-III criteria were excluded from the pooled result as this classification system adheres to a strict hierarchical rule no longer used in practice, whereby

anxiety is not diagnosed in the presence of depression. For studies that used rating scales, whatever threshold score for anxiety 'caseness' had been selected by the primary researchers was accepted. In studies that measured anxiety over more than one time point, the earliest measurement from each study was used in the meta-analysis for calculating the overall prevalence estimate. This was considered to be the most robust approximation, as it would have the largest sample size, and the most complete data. In the event that presence of anxiety was evaluated by both clinical diagnosis and anxiety rating scale, the clinical diagnosis estimate was selected for inclusion in the main results. Where multiple rating scales were administered (e.g. general anxiety distress measure such as the HADS and a scale screening for a particular type of anxiety disorder such as the Posttraumatic Diagnostic Scale), the general anxiety distress measure was reported and included in the overall results.

4.4.5 Assessing publication bias

Various forms of bias are possible that can influence the findings of a systematic review and meta-analysis. The aim of this systematic review was not to establish a causal relationship (e.g. is anxiety cause by stroke), and as such some of the types of biases reported in other types of systematic reviews would not be applicable in this case (e.g. blinding of participant and assessor). However it was thought that publication bias could be a likely problem. Reporting biases arise when the dissemination of research findings is influenced by the nature or direction of results (Sterne, Egger and Moher 2008). For example clinical trials that show a significant 'positive' effect are more likely to be published, more likely to be published rapidly, more likely to be published in English, more likely to be published more than once, and more likely to be published in high impact journals that are read and cited by others. The equivalent scenario for prevalence studies could arise, if studies that found a phenomenon to exist in a large number or people were more likely to be published than studies finding the inverse. Publication bias can be assessed by looking at the asymmetry of funnel plots. If there is no asymmetry, it is expected that larger studies with more events would lie close to the top of the line drawn for the pooled estimate and smaller studies would have only a little dispersion around the pooled estimate. Upon visual inspection this should produce a triangular shape or inverted funnel.

4.4.6 Other analyses

Correlates of anxiety reported from the included studies were assessed. This section was limited to a descriptive examination of factors that may have a significant association with anxiety after stroke. The correlates examined were reported in at least five studies. This was in line with a previous systematic review of the predictors of depression post-stroke (Hackett and Anderson 2005). Additionally a descriptive account focusing on the prevalence of post-traumatic stress disorder and symptoms was also carried out.

4.4.7 Statistical software

RevMan version 5.1 was used for all meta-analyses (The Nordic Cochrane Centre 2011).

4.5 Results

The search produced 21,432 references, of which 50 publications (from 41 studies) met the inclusion criteria in March 2010. Nine studies were translated, however only two (Ibrahimagic, Sinanovic and Smajlovic 2005; Watanabe, Koseki and Sudo 1984) met the inclusion criteria. An updated search run in March 2011, found three additional studies, giving a total of 44 studies in this review (Figure 4-1).

Ten studies which could have potentially contributed to the review findings were excluded as authors were unavailable to provide necessary information. Reasons for exclusion were: reporting anxiety as a continuous outcome (Ma, Zhang and Peng 2005; Zhang 2005; Lucev, Tadinac and Lucev 2007; Lee *et al.* 2009), using a rating scale that measured anxiety but not reporting anxiety findings (Matuja, Rwiza and Lweno 1993; Oladiji *et al.* 2009; Deng *et al.* 1999; Radziuviene *et al.* 2009), reporting only patients with co-morbid anxiety and depression (Huang 2009), reporting only correlations between anxiety and another variable (McFarlane, Hobbin and Kneebone 1987), an unpublished thesis that was not accessible (Beadle-Lindsay 1998) (Appendix A).

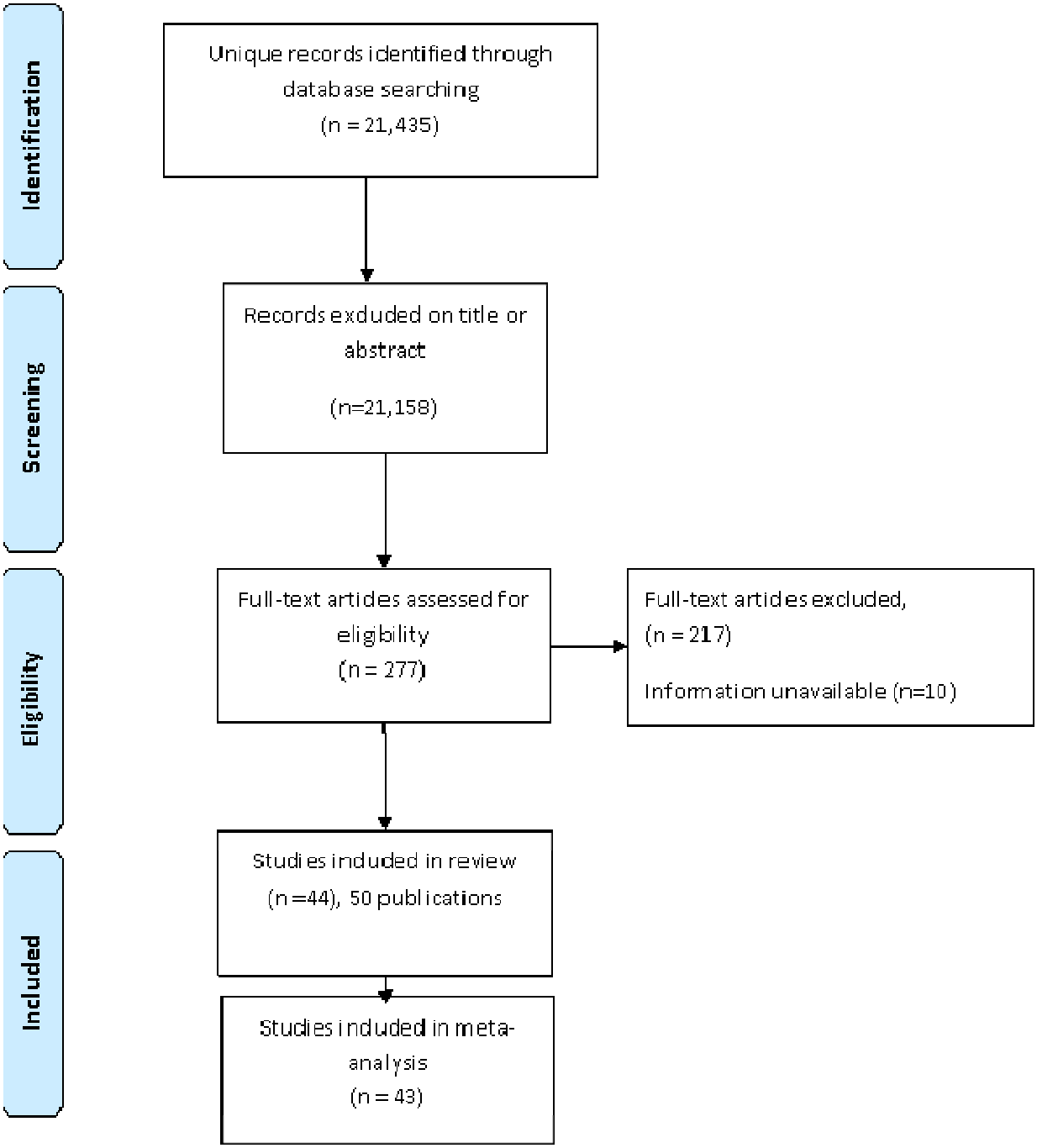


Figure 4-1 Search flow diagram

4.5.1 Study characteristics

4.5.1.1 Population-based studies

Five studies were found that included a total of 1,054 stroke survivors from a base population of 1,199,782 (House *et al.* 1991; Sharpe *et al.* 1990; Wilkinson *et al.* 1997; Ueki *et al.* 1999; Sturm *et al.* 2004; Paul *et al.* 2006; Burvill *et al.* 1995). Three studies were limited to those with first ever stroke (House *et al.* 1991; Wilkinson *et al.* 1997; Sturm *et al.* 2004), one excluded those with subarachnoid haemorrhage (Ueki *et al.* 1999), and all excluded people with major cognitive impairment, dementia or communication difficulties. Anxiety was assessed one month to five years post-stroke, and 60%-100% of eligible individuals participated. The mean age of participants ranged from 66-71 years, with males representing 51%-64% of the sample. All studies were based on assessments from patients enrolled in a local stroke registry system (Table 4-2).

4.5.1.2 Hospital, rehabilitation, and community based studies

There were 20 hospital based studies (Astrom 1996; Donnellan *et al.* 2010; Field, Norman and Barton 2008; Fure *et al.* 2006; Ibrahimagic, Sinanovic and Smajlovic 2005; Knapp and Hewison 1998; Leppavuori *et al.* 2003; Li 2006; Moon *et al.* 2004; Morris, Robinson and Raphael 1990; Morrison, Johnston and Mac Walter 2000; Morrison *et al.* 2005; Sagen *et al.* 2010; Sampson *et al.* 2003; Schultz *et al.* 1997; Stone *et al.* 2004; Townend *et al.* 2007; Raju, Sarma and Pandian 2010; Zhao 1999; Merriman, Norman and Barton 2007) which included a total of 2,163 patients. Anxiety was assessed two days to five years post-stroke. The proportion of the eligible patient population participating in the studies ranged from 52%- 89%, participation was not reported in six studies (Ibrahimagic, Sinanovic and Smajlovic 2005; Li 2006; Moon *et al.* 2004; Morris, Robinson and Raphael 1990; Watanabe, Koseki and Sudo 1984; Zhao 1999) and could not be accurately determined in one study (Schultz *et al.* 1997). The mean age of participants in hospital based studies ranged from 53-73 years, and males represented 49%-70% of the sample. Mean age was not reported in two studies (Moon *et al.* 2004; Sampson *et al.* 2003), and the gender distribution was not available in one study (Sampson *et al.* 2003).

Fourteen rehabilitation based studies which included 2,200 patients were also included in this review (Barker-Collo 2007b; Bergersen *et al.* 2010; Carod-Artal *et al.* 2009; D'Alisa *et al.* 2005; De Wit *et al.* 2008; Gangstad, Norman and Barton 2009; Ghika-Schmid *et al.* 1999; Giaquinto, Spiridigliozzi and Caracciolo 2007; Kuptniratsaikul *et al.* 2009; Masskulpan *et al.* 2008; Langhorne *et al.* 2000; Macniven *et al.* 2005; Sembi *et al.* 1998; Tang *et al.* 2002; Vickery 2006). Anxiety was assessed 10 days to 5 years post-stroke and 31%-100% of eligible patients participated in the studies although the proportion of the eligible population participating in the study was unclear in one study (D'Alisa *et al.* 2005) The mean age of the study populations ranged from 52-76 years, but was not reported in one study (Gangstad, Norman and Barton 2009). The proportion of the study population who were male in the rehabilitation based studies ranged from 45%-64%, but was not reported in three studies (Gangstad, Norman and Barton 2009; Ghika-Schmid *et al.* 1999; Sembi *et al.* 1998).

There were five community-based studies (Ahlsio *et al.* 1984; Bruggimann *et al.* 2006; Gillespie 1997; Lincoln *et al.* 1998; Visser-Keizer *et al.* 2002) which included 343 patients. Anxiety was assessed one month to two years post-stroke and 52%-82% of the eligible population participated in the studies with one study (Visser-Keizer *et al.* 2002) accounting for a third of the stroke participants in this group of studies. The mean age of the study samples ranged from 51-76 years, and the proportion who were male ranged from 59%-67%.

The participant eligibility criteria for hospital, rehabilitation and community based studies were variable. Reasons for exclusion included subarachnoid haemorrhage, previous stroke, TIA, presence of other neurological co-morbidities, pre-existing psychological problems, aphasia, and lack of competence in the native language where the study was being conducted. Table 4-2 includes a full summary of the studies included in this review.

Table 4-2 Summary of studies included the systematic review of the prevalence of anxiety after stroke

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
Oxfordshire Community Stroke Project (OCSP) (House *et al.* 1991) UK	Population/ Longitudinal cohort/ All 1st ever stroke entered in registry/ Nov 1981-Oct 1986	I: 1st ever stroke (CT) E: recurrent stroke, TIA	93% 96% 97%	71 yrs 45%	89 119 112	DSM-III (GAD)	1m 6m 1y	1.1 (0-3) 0.8 (0-3) 0
Oxfordshire Community Stroke Project (OCSP-II) (Sharpe *et al.* 1990) UK			80%	62% male	60	DSM-III-R Anxiety (ALL) Agoraphobia GAD Simple phobia Panic disorder	2-5y	 20(10-30) 8.3 (1.3-15.3) 5.0 (0-11) 5.0 (0-11) 2.0 (0-5)
Perth Community Stroke Study (PCSS) 1995 (Burvill *et al.* 1995) Australia	Population based/ Longitudinal cohort/ Ideal case finding method/ 1995-1996	I: 1st ever or recurrent stroke or TIA (WHO dfn)	60%	73 yrs (56%)	294	DSM-III* Anxiety (ALL) Agoraphobia GAD	4m	 19 (14-23) 16 (12-20) 3 (1-5)
South East London Stroke Study (SELSS) (Wilkinson *et al.*	Population/ Longitudinal cohort/	I: 1st ever stroke in persons <75 including those	70%	71 yrs median (54%)	96	HADS-A≥ 8	5y	31(22-41)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
1997) UK	All strokes recorded in register/ 1989-1990	who did not survive initial event						
North East Melbourne Stroke Incidence Study (NEMSIS) (Sturm *et al.* 2004; Paul *et al.* 2006) Australia	Population/ Longitudinal cohort/ Ideal case finding method May 1996-Apr 1999	I: 1st and recurring stroke (WHO dfn, CT or MRI)	Unclear	Unclear	475 498 201 424	IDA-A (score 9-15)	3m 1y 2y 5y	13 (10-16) 10 (7-13) 11 (6-15) 8.5 (6-11)
Hachiman Stroke Registration System (HSRS) (Ueki *et al.* 1999) Japan	Population/ Cohort/ All strokes entered in registry/ Jan-Dec 1987	I: All strokes	66%	66 yrs (64%)	47	GHQ-60-≥3 out of 7 on anx subscale	2.5y	43 (29-57)
(Astrom 1996) Sweden	Hospital/ Longitudinal cohort/ Consecutive/ Oct 1979-Jan 1981	I: Ischemic, hemorrhagic & TIA (CT) E: Congenital mental handicap	72% 78% 83% 86% 86%	73 yrs (61%)	71 70 66 57 48	DSM-III-R(GAD)	2wk 3m 1y 2y 3y	28 (18-39) 31 (21-42) 24 (14-35) 25 (13-36) 19 (7.7-30)
(Donnellan *et al.* 2010) Ireland	Hospital/ Cross-sectional/ Consecutive	I: 1st or recurrent stroke (WHO dfn, CT) & FAST ≥14, & Abbreviated	53%	Range 20-98 yrs (51%)	107 107	HADS-A≥8	1m 1y	33 (24-42) 32 (23-41)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
	admissions/ Not stated	Mental Test score ≥8 E: TIA, SAH, traumatic intracranial haemorrhage, dementia, extreme critical illness						
(Field, Norman and Barton 2008) UK	Hospital/ Cross-sectional/ Nurse approached all patients meeting inclusion criteria/ Year not stated	E: Cognitive impairment, aphasia, acute medical problems	89%	72 yrs (53%)	81	HADS-A≥11	<1m	21 (12-30)
(Fure *et al.* 2006) Norway	Hospital/ Cross-sectional/ Consecutive enrolment/ Dec 2000-Jan 2002	I: Stroke (CT) E: TIA, moderate to severe aphasia, consciousness	64%	69 yrs (63%)	178	HADS-A≥8	1wk	26 (20-33)
(Ibrahimagic, Sinanovic and	Hospital/ Longitudinal	I: Ischemic stroke (CT) and able to fill	Not stated	65 yrs (50%)	40 40	Zung≥50	2 days 2wk	30 (16-44) 25 (12-38)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
Smajlovic 2005) Bosnia	cohort/ Consecutive enrolment/ Year not state	out self report questionnaire						
(Knapp and Hewison 1998) UK	Hospital/ Cross-sectional/ Consecutive enrolment/ Year not stated	I: Stroke within past month, sufficient language and cognition to undertake long interview, named carer also willing to participate, living independently pre-stroke	Not stated	69 yrs (53%)	30 30 30	HADS-A≥8	<1m 1m post discharge 6m post discharge	47 (29-65) 27 (11-43) 30 (14-47)
(Leppavuori *et al.* 2003) Finland	Hospital/ Cross-sectional cohort/ onsecutive enrolment/ Year not stated	I: Ischemic stroke (MRI) E: SAH, ICH, no clinical neurological examination, severe apasia, refusal of psychiatric examination	57%	71 yrs (51%)	277	DSM-IV (GAD)	3-4m	21 (16-26)
(Li 2006) China	Hospital/ Cross-sectional/	I: Cerebral infarction	Not stated	53 yrs (53%)	91	HADS-A>9	Not reported	31 (21-40)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
	Random selection/ 2000-2002							
(Merriman, Norman and Barton 2007) UK	Hospital/ Cross-sectional/ In-hospital and postal-mailout to discharged patients/ Year not stated	I: ≥18 yrs & 1-12 months post stroke, able to complete self-report questionnaire E: Dysphasia, acute medical problems	52%	74 yrs (56%)	102	HADS-A≥11	1-12m	20 (12-27)
(Moon *et al.* 2004), South Korea	Hospital/ Cross-sectional/ Consecutive enrolment/ Feb- Jun 2002	I: Stroke (MRI)	Not reported	Mean age unknown (62%)	69	BAI≥22	2m	49 (37-61)
(Morris, Robinson and Raphael 1990), Australia	Hospital/ Longitudinal cohort/ Consecutive enrolment/ Year not stated	I:Ischemic & Hemorrhagic (WHO DFN, CT) E: Aphasia, however two individuals with minimal deficit included	Not reported	71 yrs (51%)	99 56	DSM-III	2m 1y	3.0 (0-6.4) 5.4 (0-11)
(Morrison, Johnston	Hospital/	I: residual	89%	69 yrs (51%)	101	HADS-A≥11	<1m	24 (15-32)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
and Mac Walter 2000; Morrison *et al.* 2005) UK	Longitudinal cohort/ Recruitment over 13 months for patients admitted to hospital/ Year not stated	disability, pass screening test for cognitive and communication problems	89% 93% 86$		78 71 38		2m 6m 3y	21 (12-29) 23 (13-32) 26 (12-40)
(Raju, Sarma and Pandian 2010) India	Hospital/ Cross-sectional/ Patients who had completed ≥1 month follow-up/ Nov 2008-Feb 2010	I: 1st ever Ischemic & Hemorrhagic stroke (WHO dfn, CT or MRI), ≥1 month post-stroke E: history of psychoactive substance abuse, dementia, psychiatric co-morbidity, aphasia	81%	54 yrs (70%)	162	HADS-A≥11	1.5y	11 (6.3-16)
(Sagen *et al.* 2010) Norway	Hospital/ Cross-sectional/ Consecutive enrolment/ Jan 2003-Jun 2005	I: Ischemic or hemorrhagic stroke E: TIA, aphasia, psychosis, MMSE <20, terminal illness	57%	65 yrs (59%)	104	DSM-IV Anxiety (ALL) GAD PTSD Social phobia Panic with Ag. Panic without Ag. Agoraphobia without Panic	4m 	 23 (15-31) 5.8 (1.3-10) 2.9 (0-6.1) 2.9 (0-6.1) 7.7 (2.6-13) 2.9 (0-6.1) 3.9 (0-7.5)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
						OCD Anxiety NOS		1.9 (0-4.6) 1.0 (0-2.8)
(Sampson *et al.* 2003) UK	Hospital/ Case-control/ Recruit from 6 stroke units/ Year not stated	I: Ischemic or hemorrhagic stroke E: Cognitive impairment, dysphasia, too physically unwell or terminal illness, MRSA infection	69%	Not reported	54	HADS-A≥10	Not reported	26 (14-38)
(Schultz *et al.* 1997) USA	Hospital/ Longitudinal cohort/ Consecutive enrolment/ Years unclear	I: Stroke	Unclear	58 yrs (57%)	142 77 79 70 66	DSM-IV (GAD)	Acute phase 3m 6m 12m 2y	19 (13-25) 22 (13-31) 25 (16-35) 11 (4.0-19) 18 (8.9-27)
(Stone *et al.* 2004) UK	Hospital/ Nested cross-sectional/ Consecutive enrolment/ Year not stated	E: Severe stroke with high risk of death, dementia, aphasia, cognitive impairment, patients living alone, carer unable to talk with researcher	71%	72 yrs median (60%)	89	HADS-A≥8	1m	20 (12-29)
(Townend *et al.*	Hospital/	I: Ischemic or	83%	76 yrs (49%)	125	HADS-A≥9	5 days	4.8 (1.1-8.6)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
2007) Australia	Longitudinal cohort/ Consecutive enrolment/ Mar-Sep 2004	hemorrhagic stroke E: Dysphagia, MMSE<20, reduced level of consciousness	95% 92%		112 105		1m 3m	8.0 (3.0-13) 14 (7.6-21)
(Watanabe, Koseki and Sudo 1984) Japan	Hospital/ Cross-Sectional/ Random selection/ Year not stated	E: aphasia, dementia	Not reported	57 yrs (57%)	35	TMAS	6m	51 (35-68)
(Zhao 1999) China	Hospital/ Cross-sectional/ Consecutive enrolment/ Year not stated	I: 1st ever stroke (Chinese Cerebral Vascular Disease Symposium of 1995 Dfn) E: Aphasia, mental disorder, epilepsy, mental retardation, cerebral trauma	Not reported	63 yrs (61%)	206	Zung SAS≥50	1m	18 (13-24)
(Barker-Collo 2007b) New Zealand	Rehabilitation/ Cross-Sectional/ Consecutive/ Not stated	I: Ischemic, Hemorrhagic (CT) E: Aphasia, non-native language speaker	81%	52 yrs (55%)	73	BAI≥26	3m	21 (11-32)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
(Bergersen *et al.* 2010) Norway	Rehabilitation/ Cross-Sectional/ Mail-out all patients/ 1998-2001	I: Ischemic, ICH, SAH E: Aphasia	64%	58 yrs (64%)	162	HADS-A≥11	2-5y	17 (11-22)
(Carod-Artal *et al.* 2009) Brazil	Rehabilitation/ Cross-sectional/ Consecutive enrolment/ Jul 2007-Jun 2008	I: Ischemic & hemorrhagic (Clinical dx and radiological findings) E: TIA, subdural haematoma, dementia, aphasia, severe disability due to previous neurological disorder	77%	56 yrs (52%)	300	HADS-A≥11	20m	24 (19-29)
(D'Alisa *et al.* 2005) Italy	Rehabilitation/ Cross-sectional/ Consecutive enrolment/ Not stated	E:MMSE <24, Aphasia	unclear	63 yrs (60%)	73	HADS-A≥11	5y	21 (11-30)
(De Wit *et al.* 2008) England, Belgium, Switzerland,	Rehabilitation/ Longitudinal cohort/ Consecutive	I: 1st ever stroke (WHO criteria- CT), RMA-GF≤11 and/or Leg Trunk	95% 95% 92%	70 yrs (53%)	491 478 467	HADS-A≥8	2m 4m 6m	25 (21-29) 23 (19-27) 21 (18-25)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
Germany	enrolment/ Mar 2002- Sep 2004	function ≤8 and/or Arm function ≤12 E: neurological impairments, pre-stroke BI<50, subdural hematoma, admitted to rehab centre ≥6 wks post-stroke						
(Gangstad, Norman and Barton 2009) UK	Rehabilitation/ Cross-sectional/ All patients attending clinic approached meeting inclusion approached/ Study conducted over 6 months	E: Cognitive impairment	100%	Not reported	15	HADS-A≥11	14m	6.7 (0-19)
(Ghika-Schmid *et al.* 1999) Switzerland	Rehabilitation/ Cross-sectional/ Consecutive enrolment/ Year not stated	I: 1st ever stroke only (CT or MRI)	72%	60 yrs (not provided)	31	HAM-A>14	3m	29 (13-45)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
(Giaquinto, Spiridigliozzi and Caracciolo 2007) Italy	Rehabilitation/ Cross-sectional/ Consecutive enrolment/ 2004-2005	I: 1st ever stroke only (CT or MRI) E: TIA, SAH, previous stroke but not TIA, admission to rehab>3 weeks post-stroke, severe co-morbidity, mental or comprehension impairment	81%	70 yrs (46%)	132	HADS-A≥6	10 days	42 (33-50)
(Masskulpan *et al.* 2008; Kuptniratsaikul *et al.* 2009) Thailand	Rehabilitation/ Longitudinal cohort/ National registry from consecutive enrolled patients/ Mar-Dec 2006	I: Stroke patients ≥18 yrs E: Severe medical comorbidities, Inability to communicate, dementia, schizophrenia or present psychotic episode	Not stated 77%	62 yrs (59%)	327 251	HADS-A≥11	~24 days 2m	5.8 (3.3-8.4) 26 (20-31)
(Langhorne *et al.* 2000) UK	Rehabilitation/ Prospective longitudinal cohort/ Multi-centre	I: Stroke (WHO dfn) within 7 days of onset	71% 82% 86%	76 yrs (52%)	220 181 155	Single Question	6m post discharge 18m post discharge 30m post	34 (28-40) 44 (37-51)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
	consecutive enrolment/ 7 months						discharge	49 (41-57)
(Macniven *et al.* 2005) UK	Rehabilitation/ Cross-sectional/ 2 week audit of all patients on ward/ Year not stated	E: Language problems	57%	68 yrs (47%)	17	HADS-A≥8	58.5 days	65 (42-87)
(Sembi *et al.* 1998) UK	Rehabilitation/ Cross-sectional/ Recruited from 3 rehab sites/ Jan 1995-Apr 1996	I: >18 yrs with 1st ever stroke or TIA, able to complete self-report questionnaire E: Dysphasia	77%	66 yrs (% male not reported)	61	HADS-A≥11	18m	15 (5.9-24)
(Tang *et al.* 2002) Hong Kong	Rehabilitation/ Cross-sectional/ Consecutive enrolment/ Jun 1999-Aug 2000	I: 1st ever stroke (CT) E: TIA, SAH, history of neurological impairment, comprehension and communication deficits, length of stay <2 wks	31%	71 yrs (45%)	157	DSM-III-R	25 days	0.6 (0-1.9)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
(Vickery 2006) USA	Rehabilitation/ Cross-sectional/ Sample of admitted patients/ Year not stated	I: Stroke E: history of co-morbid dementia, non-stroke neurological process, acute delirium, severe psychiatric disturbance	90%	69 yrs (45%)	141	AMAS ≥65	20 days	7.8 (3.4-12)
(Ahlsio *et al.* 1984) Sweden	Community/ Cross-Sectional/ Consecutive enrolment/ Jan-Dec 1979	I: CI, TIA, SAH (CT) E: Severe disability, aphasia, dementia	55%	71 yrs, (60%)	53	Self Report	2y	26 (15-38)
(Bruggimann *et al.* 2006) Switzerland	Community/ Cross-sectional/ Consecutive enrolment/ Year not stated	I: 1st ever Ischemic or Hemorrhagic stroke E: NIHSS>3, history of psychiatric illness, neurologic co-morbidity	52%	51 yrs (67%)	49	HADS-A≥8	1y	24 (12-37)
(Gillespie 1997) UK	Community/ Cross-sectional/ Registry mailout to discharged	I: Stroke (WHO dfn) E: Communication difficulties, cognitive impairment,	68%	69 yrs (66%)	44	HADS-A≥9	7m	25 (12-38)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent with Anxiety (95% CI)
	patients/ Year not stated	significant co-morbidity, recent experience of major life event unrelated to stroke						
(Lincoln *et al.* 1998) UK	Community/ Cross-sectional/ 74 GP practices/ Aug 1994-Aug 1996	I: Stroke (WHO dfn)	82%	76 yrs (67%)	84	HADS-A≥11	1m	26 (17-36)
(Visser-Keizer *et al.* 2002) Netherlands	Community/ Cross-sectional/ 350 GP clinics/ Year not stated	I: 1st ever ischemic stroke (CT) E: neurologic or psychiatric history, history of alcohol or drug abuse, insufficient language and cognitive ability to allow assessment, aphasia	61%	67 yrs (59%)	113	HADS-A≥6	3m	14 (7.7-21)

AMAS: Adult Manifest Anxiety Scale, CI: Cerebral Infarction, CT: Computer Tomography used to diagnose stroke, DSM: Diagnostic and Statistical Manual of Mental Disorders, FAST: Frenchay Aphasia Screening Test , GAD: Generalized Anxiety Disorder, HADS-A: Hospital Anxiety and Depression Scale Anxiety Subscale, HAM-A: Hamilton Anxiety Scale, ICH: Intracerebral Hemorrhage, IDA-A: Irritability Depression and Anxiety Scale, Anxiety subscale, MMSE: Mini Mental State Examination, MRI: Magnetic Resonance Imaging used to diagnose stroke, NIHSS: National Institute of Health Stroke Scale, OCD: Obsessive Compulsive Disorder, PTSD: Post-Traumatic Stress Disorder SAH: Subarachnoid Hemorrhage, TIA: Transient Ischemic Attack, TMAS: Taylor Manifest Anxiety Scale, WHO DFN: World Health Organization definition of stroke, Zung SAS: Zung Self Rating Anxiety Scale

4.5.1.3 Measurement and assessment of anxiety

Clinical diagnoses of anxiety disorders were made in eight studies in accordance with different versions of the DSM. The DSM-III (American Psychiatry Association 1980) was used in three studies (House *et al.* 1991; Burvill *et al.* 1995; Morris, Robinson and Raphael 1990), while three studies(Astrom 1996; Sharpe *et al.* 1990; Tang *et al.* 2002), used the DSM-III-R.(American Psychiatric Association 1987). The Oxfordshire Community Stroke Project (OCSP) used the DSM-III-R for its long-term follow-up assessment so it is included in both the DSM-III and DSM-III-R categories. Another three studies (Leppavuori *et al.* 2003; Sagen *et al.* 2010; Schultz *et al.* 1997), used the DSM-IV (American Psychiatric Association 1994). Table 4-3 provides an overview of the eight different standardised scales that were used to identify anxiety symptoms. One study used a single question measure (Langhorne *et al.* 2000), and another used a series of five researcher developed questions to identify anxiety (Ahlsio *et al.* 1984).

Table 4-3 Synopsis of rating scales used to measure anxiety symptoms

Screening tool	Details	No. studies	Suggested threshold scoring	Cut-off scores reported from studies
Adult Manifest Anxiety Scale (AMAS)(Reynolds, Richmond and Lowe 2003)	Self report scale with 36 to 44 items. Total number of anxiety items endorsed is summed and converted to an age-referenced T-score	1	Age dependent	T-score ≥65
Beck Anxiety Inventory (BAI)(Beck *et al.* 1988)	Self-report 21 item scale that discriminates between anxiety and depression. Possible score ranges from 0-63.	2	0-7 minimal 8-15 mild 16-25 moderate 26-63 severe anxiety	≥16, >22
General Health Questionnaire-60 (GHQ-60) (Goldberg D and Williams P 1988)	A 60 item scale used to screen for various aspects of psychiatric distress. Includes an anxiety subscale.	1	Determined by researcher	≥3 out of 7 on anxiety subscale
Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1969)	Clinician administered 14 item scale designed to assess anxiety symptoms not specific to any disorder, however widely used as an outcome measure of GAD in therapeutic trials. It measures specific anxiety symptom clusters that are both psychic and somatic (e.g. tension, insomnia, respiratory). Possible scores range from 0-56	1	<17 mild 18-24 mild to moderate ≥25 severe anxiety	>14
Hospital Anxiety and Depression Scale, Anxiety subscale (HADS-A) (Zigmond and Snaith 1983)	Self-report 14 item scale divided into two subscales, used to screen for psychic anxiety and depression symptoms in medically compromised patients. Possible score ranges from 0-21 on each subscale.	25	0-7 minimal 8/9 possible anxiety disorder 10/11 probable anxiety disorder.	≥6, ≥8, ≥9, ≥10, ≥11
Irritability Depression and Anxiety, Anxiety subscale (IDA-A) (Snaith *et al.* 1978)	Self report scale with 5 items anxiety subscale. Possible scores range from 0-15	1	0-8 minimal to mild 9-15 moderate to severe anxiety	≥9
Taylor Manifest Anxiety Scale (TMAS) (Taylor 1951)	Clinician administered 50 item scale. Possible scores range from 0-50 with higher score indicative of higher levels of trait anxiety.	1	14/15 indicative of anxiety, differential sex based thresholds recommended	>23 for males, >26 females
Zung Self Rating Anxiety Scale (William and Zung 1971)	Self report 20 item scale with measures of state and trait anxiety. Possible scores range from 20-80	2	20-44 normal 45-59 mild to moderate 60-74 severe 75-80 extreme	≥50

4.5.2 Anxiety Prevalence

4.5.2.1 Anxiety disorders

Overall prevalence of anxiety disorders after stroke was 18% (95%CI 8%-29%, [I^2=97%, p<0.001]). Although the Perth Community Stroke Study (PCSS) used the DSM-III it did not apply the hierarchical diagnostic rule, so it has been included in the meta-analysis. One study (Tang *et al.* 2002) with an unusually low prevalence estimate contributed all of the heterogeneity of the I^2 statistic, and the prevalence of anxiety disorders excluding this study was 20% (95%CI 18% - 23%, [I^2=0%, p=0.65]).

Three studies (Sharpe *et al.* 1990; Sagen *et al.* 2010; Burvill *et al.* 1995), measured different types of anxiety and found that phobic disorders (range 13-16%) then GAD (range 3-6%) were the two most common. One study also reported that 3% of their study sample had Post-Traumatic Stress Disorder (Sagen *et al.* 2010). Three studies (Astrom 1996; Leppavuori *et al.* 2003; Schultz *et al.* 1997) looked exclusively at GAD after stroke, with all three reporting a prevalence of approximately 20%. One study that looked exclusively at GAD, differentiated between primary GAD and GAD due to stroke (Leppavuori *et al.* 2003), and found that just over half of the anxiety cases received a primary diagnosis.

4.5.2.2 Anxiety symptoms assessed by rating scale

The overall frequency of anxiety symptoms or 'caseness' as assessed by rating scale was 24% (95% CI 21%-28%, [I^2=91%, p<0.001]) (Figure 4-3). The prevalence of anxiety symptoms post-stroke did not differ significantly from that of anxiety disorder after stroke (X^2=1.16, df=1, p=0.28).

The HADS-A was the most commonly utilised rating scale for assessing anxiety 'caseness', having been used in 74% of studies (Table 4-3). The majority of these studies used a HADS-A cut off of 8/9 or 10/11 to define 'possible' or 'probable' anxiety. Studies using a lower cut-off on the HADS-A reported statistically significant higher prevalence rates relative to those using the 'probable' threshold: ([28%, 95%CI 19-36] vs [19%, 95%CI 13-24%], I^2= 79%, p=0.03).

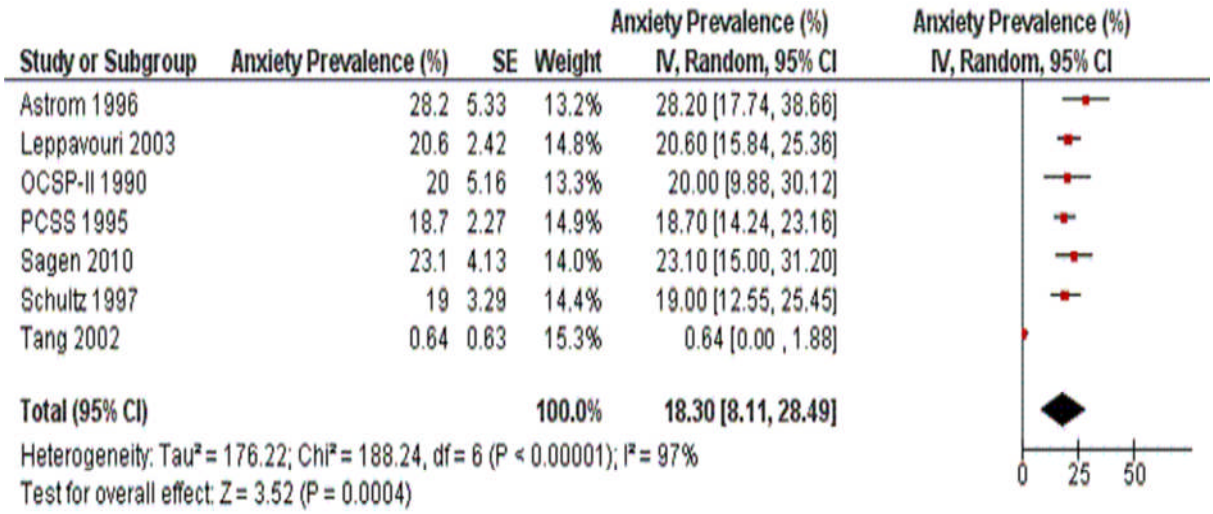


Figure 4-2 Prevalence of anxiety disorders after stroke (random effects model)

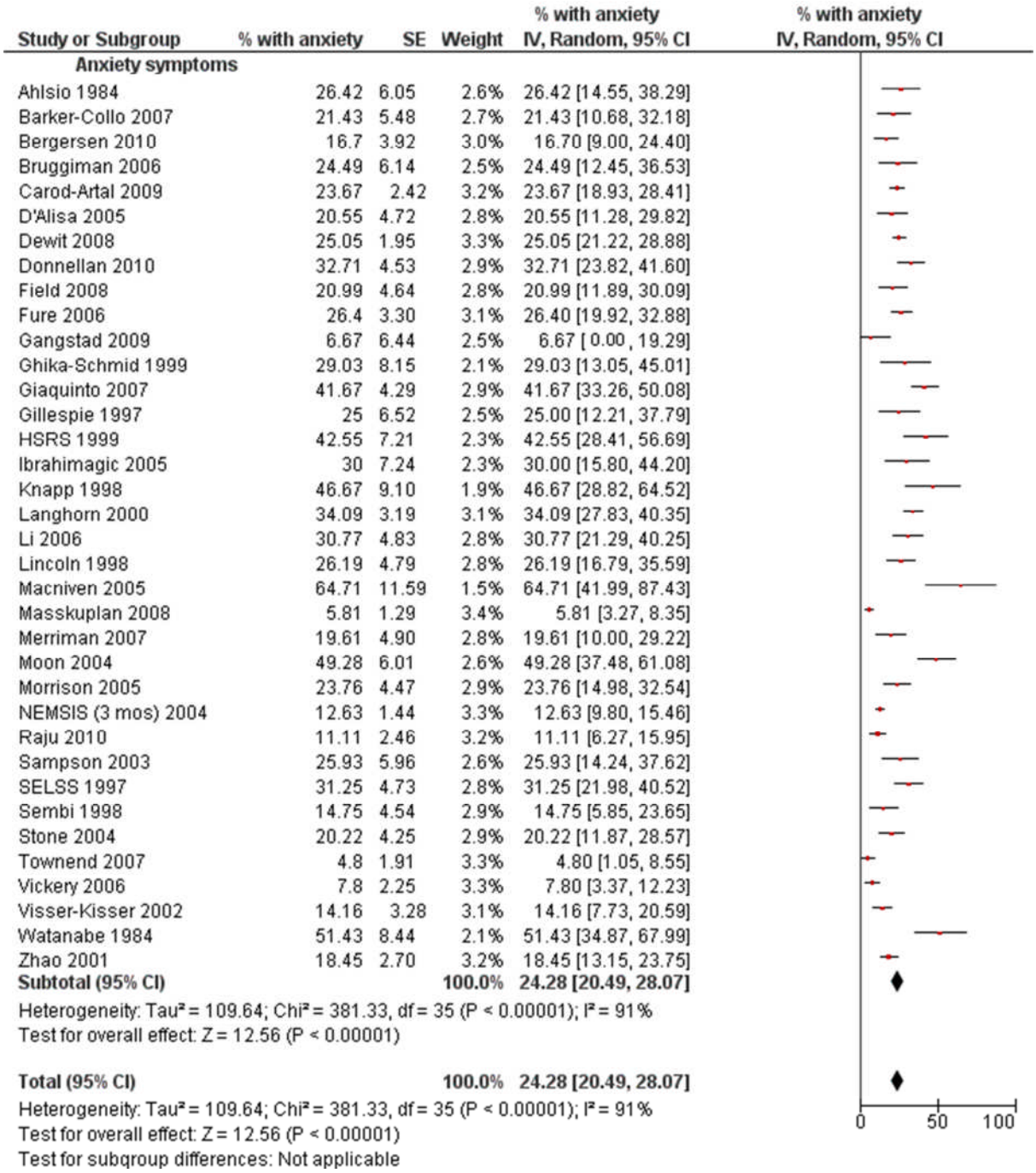


Figure 4-3 Prevalence of anxiety symptoms after stroke (Random Effect Model)

4.5.3 Time Course, Co-morbidity and clinical factors

As the rates of anxiety reported by clinical interview and rating scales did not differ statistically, all data were combined to assess the prevalence of any type of anxiety in the remaining analyses. An analysis stratified by time post-stroke and source of population was conducted to compare findings from this review with a previously published review on depression after stroke which is discussed in section 4.6.1. Table 4-4 shows there was there was a non-significant increase in the prevalence of anxiety over time. Overall frequency was 20% (95% CI 13%-26%, [I^2= 96%, p<0.001]) in the acute phase; 23% (95% CI 19%-27%, [I^2= 84%, p<0.001]) 1-5 months post-stroke; and 24% (95%CI 19%-29%, [I^2=89%, p<0.001]) 6 months or more post-stroke. The acute phase rehabilitation and midterm population based study subgroups had the lower anxiety prevalence, relative to the other stratified sub groups (Table 4-4). There were no differences in anxiety prevalence when stratified by source of study population, with pooled prevalence estimates ranging from 21 to 25%.

Table 4-4 Anxiety prevalence estimates by time post-stroke and source of study population

	n- number of studies, N- number of participants	% with anxiety (95%CI) Random Effects Model	I^2	Significance of heterogeneity
Less than one month	n=12; N= 1525	20 (13-26)	96%	<.001
Hospital studies	n=8, N= 768	13 (4-21)	97%	<.001
Rehabilitation studies	n=4, N= 757	24 (15-33)	90%	<.001
1-5 months	n=19; N= 3001	23 (19-27)	84%	<.001
Population	n=2, N= 769	15 (9-21)	80%	0.02
Hospital	n=10, N= 1189	24 (18-30)	85%	<.001
Rehab	n=5, N= 846	28 (21-34)	67%	0.02
Community	n=2, N= 197	20 (8-31)	77%	0.04
≥ 6 months	n=22, N= 2797	24 (19-29)	89%	<.001
Population	n=4, N= 701	26 (7-45)	98%	<.001
Hospital	n=8, N= 652	26 (18-34)	81%	<.001
Rehab	n=7, N= 1298	21 (16-26)	76%	<.001
Community	n=3, N= 146	25 (18-32)	0%	0.97

Three studies examined the time course of anxiety within individual stroke patients. The Collaborative Evaluation of Rehabilitation in Stroke across Europe study (De Wit *et al.* 2008) found that 40% of patients with anxiety two months after stroke, remained anxious four months later, and 7-11% of patients not anxious at two months became so two to four months later. The population-based Perth Community Stroke Study (Burvill *et al.* 1995) found that 16% of patients with anxiety disorder at four months post-stroke, remained anxious eight months later. A similar trend was observed in a small study by Astrom (Astrom 1996), who reported that after three years post-stroke 62% of patients with early onset GAD had not recovered, however the small sample size from this last study mean results should be interpreted with caution.

Three studies (Burvill *et al.* 1995; Sembi *et al.* 1998; Leppavuori *et al.* 2003) reported pre-stroke mood disorders and found that approximately one third of patients with post-stroke anxiety had a history of pre-stroke mood or anxiety disorder. Ten studies reported co-morbidity of anxiety and depression (Astrom 1996; Barker-Collo 2007b; Bergersen *et al.* 2010; Donnellan *et al.* 2010; Leppavuori *et al.* 2003; Macniven *et al.* 2005; Sagen *et al.* 2010; Schultz *et al.* 1997; Fure *et al.* 2006; Burvill *et al.* 1995), and found that 17-80% of those with anxiety also had depression. No study reported whether stroke patients received any form of treatment for their anxiety. Additionally, two population-based studies with community-matched controls found no difference in anxiety prevalence rates between stroke and non-stroke patients (Burvill *et al.* 1995) (House *et al.* 1991).

Data were stratified by studies conducted in samples of first-ever stroke only, and compared with studies whereby individuals with recurrent strokes were included. Thirteen studies included those with first ever stroke only, while 29 studies consisted of individuals who had one or more strokes. No significant difference was observed in the prevalence of anxiety between those with first ever stroke [21% (95% CI 13-28%), I^2=97%] compared to those with recurrent stroke [25% (95%CI 21-29%), I^2= 90%], X^2=0.81, df=1, p=0.37].

4.5.4 Quality of evidence

Table 4-5 provides a summary of the quality indices of each study included in the review. The following sub-section describes their influence on the observed prevalence of anxiety after stroke.

Table 4-5 Summary table of quality of evidence

Author	Unbiased recruitment	Internal Validity	Response Rate Reported	Response ≥60%	External Validity	Funding source reported	No conflicts
Ahlsio 1984	x	?	√	x	√	x	√
Astrom 1996	x	√	√	√	√	√	√
Barker-Collo 2007	x	**	√	√	√	x	√
Bergerssen 2010	x	**	√	√	√	√	√
Bruggiman 2006	x	**	√	x	√	√	√
Carod-Artal 2009	x	**	√	√	√	x	√
D'Alisa 2005	x	**	x	?	√	x	√
DeWit 2008	x	**	√	√	√	√	√
Donellan 2010	x	**	√	x	√	x	√
Field 2008	x	**	√	√	√	x	√
Fure 2006	x	**	√	√	√	x	√
Gangstad 2009	x	**	√	√	√	x	√
Ghika-Schmid 1999	x	**	√	√	√	x	√
Giaquinto 2007	x	**	√	√	√	x	√
Gillespie 1997	x	**	√	√	√	x	√
HSRS 1999	√	**	√	√	x	x	√
Ibrahimagic 2005	x	**	x	?	x	x	√
Knapp 1998	x	**	x	?	√	√	√
Kuptniratsaikul 2008	x	**	?	√	√	√	√
Langhorne 2000	x	?	√	√	√	√	√
Leppavuori 2003	x	√	√	x	√	√	√
Li 2006	x	**	x	?	√	x	√
Lincoln 1998	x	**	√	√	√	√	√
Macniven 2005	x	**	√	√	√	x	√
Merriman 2007	x	**	√	x	√	x	√
Moon 2004	x	**	x	?	x	x	√
Morris 1990	x	√	√	√	√	√	√
Morrison 2000/05	x	**	√	√	√	√	√
NEMSIS 2004	√	**	√	√	√	√	√
OCSP 1990/91	√	√	√	√	√	√	√
PCSS 1995	√	√	√	√	√	√	√
Raju 2010	x	**	√	√	√	√	√
Sagen 2010	x	√	√	√	√	√	√
Sampson 2003	x	**	√	√	x	x	√
Schultz 1997	x	√	√	x	√	√	√
SELSS 1997	√	**	√	√	√	√	√
Sembi 1998	x	**	√	√	√	√	√
Stone 2004	x	**	√	√	√	√	√
Tang 2002	x	√	√	x	√	√	√
Townend 2007	x	**	√	√	√	√	√
Vickery 2006	x	**	√	√	√	x	√
Visser-Keizer 2002	x	**	√	x	√	√	√
Watanabe 1984	x	**	x	?	√	x	√
Zhao 1999	x	**	x	x	√	x	√

√- Yes	x- No	?- Unclear	**- Possible

4.5.4.1 Method of recruitment

Method of recruitment into studies was variable (Figure 4-4). Estimating post-stroke anxiety prevalence from individuals enrolled in a comprehensive registry system established in a geographic locale was considered the gold standard method of recruitment. Five population based studies used this method. The majority of studies (n=25) used consecutive patient recruitment strategy, whereby all patients admitted to hospital or rehabilitation unit over a specified period of time were eligible for participation in the study. There was variability in other methods of recruitment into study that included postal questionnaires (n=3), random selection (n=2), selective GP practices (n=2), a selective approach such as recruiting patients who completed more than one month of rehabilitation (n=4), clinical audit (n=1), and case-control study (n=1). One study(Sembi *et al.* 1998) did not explicitly describe the method of recruitment (Figure 4-4).

Prevalence rates were similar across all methods of recruitment with the exception of two Chinese studies (Li 2006; Watanabe, Koseki and Sudo 1984) using random selection and one UK study (Macniven *et al.* 2005) which was a clinical audit reporting higher prevalence estimates.

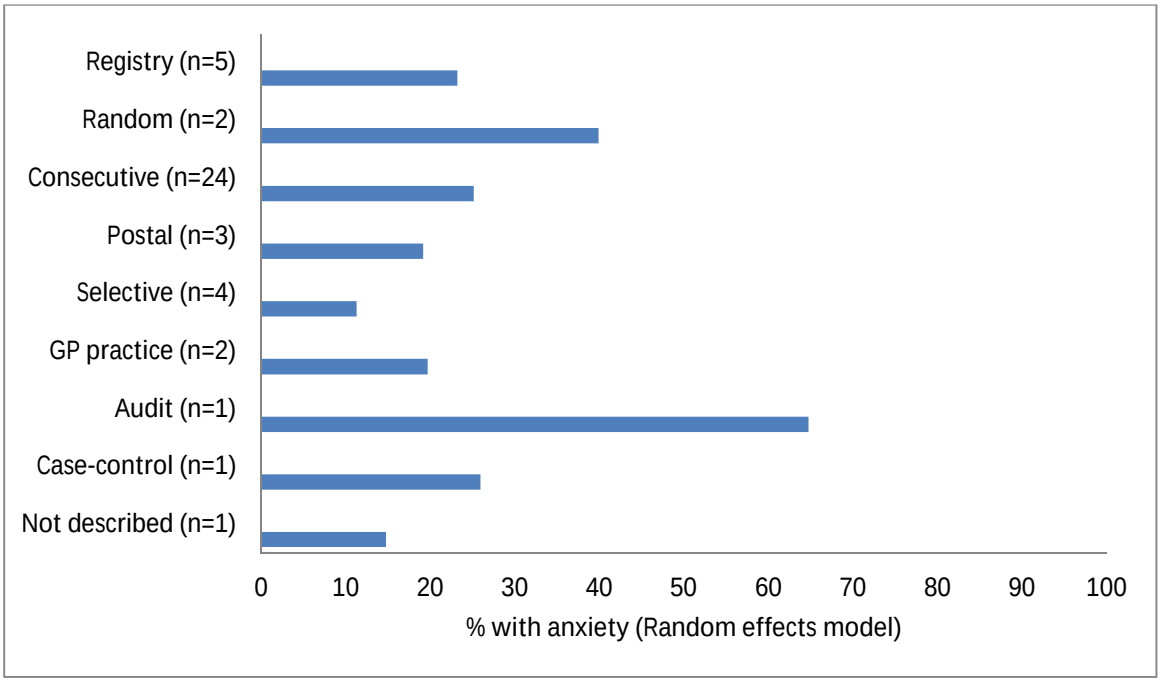


Figure 4-4 Anxiety prevalence stratified by method of recruitment

4.5.4.2 Diagnostic or Screening tool

Multiple versions of the DSM and various anxiety symptom rating scales were used among studies. Due to the hierarchical exclusionary principal whereby anxiety was not diagnosed in the presence of other mood disorders, diagnosis of anxiety disorders was lowest among studies using the DSM-III. The prevalence estimates based on the Adult Manifest Anxiety Scale, and the Irritability Depression and Anxiety scale, were lower as well (Table 4-6).

Table 4-6 Anxiety prevalence stratified by diagnostic/ rating scale

Diagnostic/ Rating Scale	N- number of studies, N- number of participants	% with anxiety (95%CI) Random Effects Model	I^2	P for heterogeneity
DSM-III	N=2, n= 188	1.7 (0-3.5)	0%	0.35
DSM-III-R	N=4, n=582	16 (3-30)	97%	<.001
DSM-IV	N=3, n= 523	21 (17- 24)	0%	0.74
HADS-A ≥6	N=2, n= 245	28 (1-55)	96%	<.001
HADS-A ≥8/9	N=10, n= 1226	28 (19-36)	92%	<.001
HADS-A ≥10/11	N=13, n=1613	19 (13-24)	87%	<.001
AMAS	N=1, n= 141	7.8 (0-27)	-	-
BAI	N=2, n= 142	35 (8-63)	91%	<.001
GHQ-60 (≥3 on anxiety subscale)	N=1, n= 47	43 (29-57)	-	-
HAM-A	N=1, n= 31	29 (13-45)	-	-
IDA-A	N=1, n=475	13 (10-16)	-	-
TMAS	N=1, n= 35	51 (35-68)	-	-
Zung	N=2, n= 246	22 (12-33)	55%	0.14

AMAS: Adult Manifest Anxiety Scale, BAI: Beck Anxiety Inventory, DSM-III: Diagnostic and Statistical Manual of Mental Disorders Third Edition, DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders Third Edition-Revised, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, GHQ-60: General Health Questionnaire-60, HADS-A: Hospital Anxiety and Depression Scale-anxiety subscale, HAM: Hamilton Anxiety Rating Scale, IDA-A: Irritability Depression and Anxiety Scale-anxiety subscale, TMAS: Taylor Manifest Anxiety Scale, Zung: Zung Self Rating Anxiety Scale

4.5.4.3 Response rate and lost-to follow-up

A response rate greater than or equal to 60% participation by the eligible population was considered satisfactory. The majority of studies (n=29) had recruitment rates whereby 60% or more of the eligible population was included in the study. Nine studies did not achieve the 60% criteria, and the rate was unclear in six studies. Prevalence estimates varied based on the proportion of eligible participants that participated in studies. There was no significant difference in prevalence between studies with satisfactory participation compared with studies where less than 60% of the eligible population participated: (21%, 95%CI 17-25%) vs. (25%, 95%CI 13-37%), X^2= 0.46, df=1, p=0.53. However, studies whereby it was unclear how many of the eligible patients participated in the study, had significantly higher anxiety prevalence (32%, 95%CI 23-40%).

For longitudinal studies loss to follow-up less than 40% was deemed adequate for maximal quality assessment score. None of the studies with longitudinal follow-up lost more than 40% of their sample at the subsequent time-point.

4.5.5 Publication bias

A few small studies (Knapp and Hewison 1998; Macniven *et al.* 2005; Moon *et al.* 2004; Ueki *et al.* 1999; Watanabe, Koseki and Sudo 1984)with larger standard error contributed substantially to the funnel plot asymmetry. The funnel plot revealed more asymmetry amongst studies with lower cut-off scores on the HADS scale relative to those using the 'probable' threshold, indicating possible publication bias in favour of studies with higher prevalence estimates (Figure 4-5).

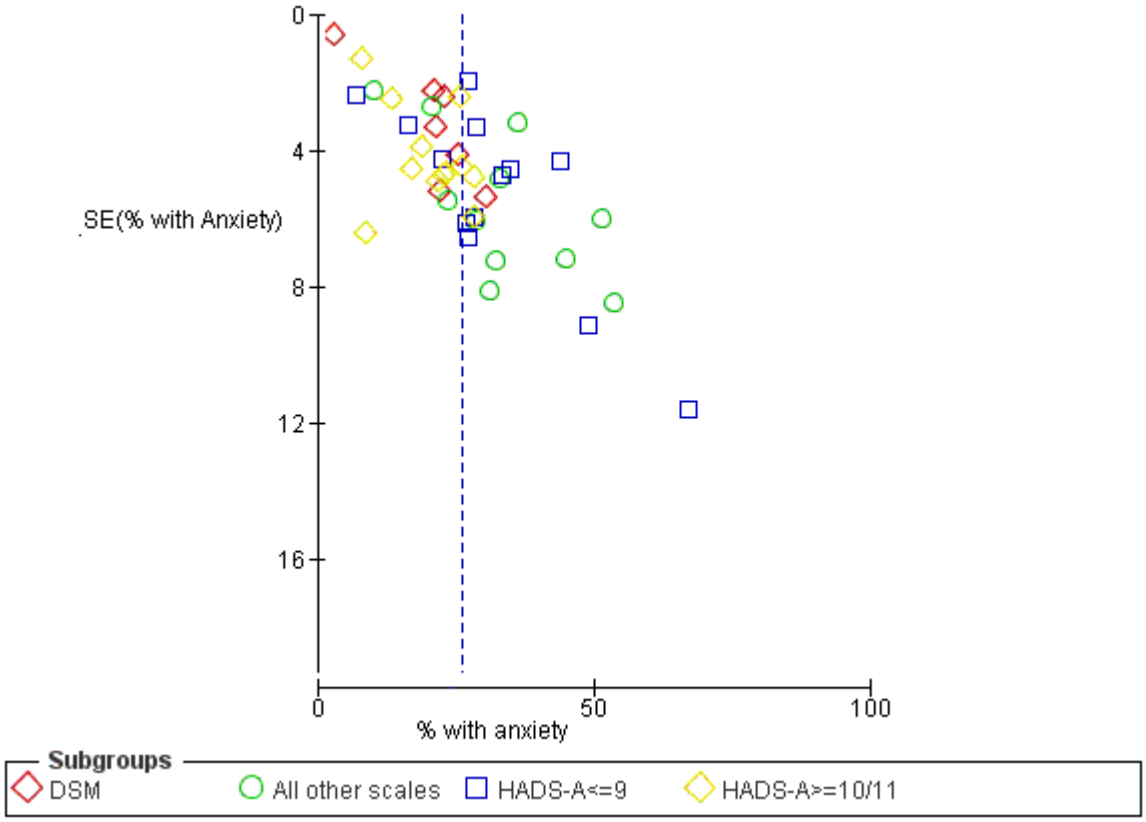


Figure 4-5 Funnel plot of anxiety prevalence stratified by method used to assess anxiety

4.5.6 Correlates of anxiety after stroke

Investigating anxiety was rarely a primary aim of the studies included in this review and factors that may have be associated with anxiety were inconsistently reported. The variables correlated with anxiety and described in this section are those that were reported in five or more studies.

4.5.6.1 Activities of daily living

Findings were mixed for activities of daily living. Three studies (Leppavuori *et al.* 2003; Astrom 1996; Fure *et al.* 2006) reported a significant negative correlation and four studies (Morrison *et al.* 2005; Sagen *et al.* 2010; D'Alisa *et al.* 2005; Masskulpan *et al.* 2008) found no significant association with anxiety after stroke.

4.5.6.2 Age

There was no significant association observed between age and anxiety after stroke in 6 of 8 studies (Astrom 1996; Barker-Collo 2007b; Leppavuori *et al.* 2003; Li 2006; Sagen *et al.* 2010; Fure *et al.* 2006), however two studies (Carod-Artal *et al.* 2009; Raju, Sarma and Pandian 2010) reported significant negative correlations between age and anxiety.

4.5.6.3 Depression

There was a significant positive association between depression and anxiety in all six studies (Schultz *et al.* 1997; Carod-Artal *et al.* 2009; Gillespie 1997; Kuptniratsaikul *et al.* 2009; Leppavuori *et al.* 2003; Morrison *et al.* 2005) in which it was assessed.

4.5.6.4 Gender

There was no significant association observed between gender and anxiety after stroke in five of seven studies (Astrom 1996; Barker-Collo 2007b; Carod-Artal *et al.* 2009; Leppavuori *et al.* 2003; Sagen *et al.* 2010), however two studies (Schultz *et al.* 1997; Li 2006) reported a significant positive asociation between being female and having anxiety after stroke

4.5.6.5 Lesion location

There was no significant association observed between stroke lesion location and anxiety after stroke in 5 of 6 studies (Sharpe *et al.* 1990; Astrom 1996; Barker-Collo 2007b; Fure *et al.* 2006; Ghika-Schmid *et al.* 1999; Leppavuori *et al.* 2003).

4.5.6.6 Quality of life

Four of five studies (Moon *et al.* 2004; Ahlsio *et al.* 1984; Donnellan *et al.* 2010; Kuptniratsaikul *et al.* 2009; Raju, Sarma and Pandian 2010) found a significant negative correlation with quality of life.

4.5.7 Post-Traumatic Stress Symptoms

Post-traumatic stress disorder (PTSD) after stroke is not well established in research or clinical practice. However as it is an emerging area of interest, the findings from the studies where it was examined have been summarised separately.

This review found five studies (Bruggimann *et al.* 2006; Field, Norman and Barton 2008; Merriman, Norman and Barton 2007; Sampson *et al.* 2003; Sembi *et al.* 1998) that in addition to administering a global measure of anxiety distress such as the HADS, also examined the occurrence of post-traumatic stress symptoms. These stress symptoms will be referred to using the post-traumatic stress disorder (PTSD) label. However it is acknowledged that a PTSD rating scale does not diagnose this mental health condition and only gives an indication of individuals who could be considered for additional investigation by a mental health professional (e.g. psychiatrist or psychologist). Three different rating scales were used to measure PTSD:

1. The Impact of Event Scale (IES) (Horowitz, Wilner and Alvarez 1979) assesses intrusive thoughts and avoidant behaviour associated with PTSD.
2. The Post-Traumatic Distress Scale (PDS) (Foa *et al.* 1997) assesses all the DSM-IV criteria for PTSD.
3. The Post-Traumatic Stress Disorder Checklist- specific (PCL-S) (Weathers, Litz and Herman 1993) is a 17 item self-report scale that corresponds to the DSM-III-R symptoms of PTSD.

One study(Sembi *et al.* 1998) administered the IES and the Penn Inventory of PTSD (Penn) (Hammarberg 1992) scale and then followed up patients scoring within the PTSD-symptom range on either scale with a clinician administered PTSD scale (CAPS).

Prevalence of PTSD symptoms as assessed by a rating scale ranged from 6-31%. The one study (Sembi *et al.* 1998) that followed up nine patients scoring within the PTSD symptom range with a clinician-administered interview, found that six (66%) could be defined as having PTSD. This represented 10% of the overall study sample. The pooled prevalence estimate of PTSD symptoms was 12% (95% CI 9%- 16%), I^2= 76%, p=.002.

All five of these studies conducted correlation analyses to identify clinical factors that were potentially associated with PTSD symptoms. Given the limited number of studies, no clear conclusions could be drawn. However age and gender were consistently reported in all five studies. Findings were mixed for age with two studies (Field, Norman and Barton 2008; Sampson *et al.* 2003) reporting a significant negative correlation between age and PTSD, and three studies finding no association. A similar trend was observed with gender.

Two studies (Sampson *et al.* 2003; Bruggimann *et al.* 2006) reported a significant positive correlation between female gender, whereby no association was observed in the remaining three studies (Table 4-7).

Table 4-7 Summary of studies assessing PTSD after stroke

Study author, Year published	N	Criteria	Time post Stroke	Percent with PTSD	Factors Associated with PTSD
(Bruggimann *et al.* 2006)	49	IES	1 yr	31%	(+): Female gender, Anxiety, Depression, Subjective trauma (n.s.): Neurological deficit, memory score, Lesion location, Age
(Field, Norman and Barton 2008)	81	PDS	<1 mos 3 mos	Mean = 9.32, SD=8.73 Mean = 11.9, SD=10.47	(+):Anxiety, Depression, Negative cognitions about self & the world (-): Age (n.s.): Gender, Marital status, Education, #of previous strokes, Time since stroke, Consciousness at time of stroke, Self blame
(Merriman, Norman and Barton 2007)	102	PDS	1-12 mos	16% (Mean = 11.22, SD=4.30)	(+): Previous stroke, cognitive appraisal, Anxiety, Depression, Negative affect (-): Time since stroke (n.s.): Age, Gender, Marital status, Lesion location, Barthel Index
(Sampson *et al.* 2003)	54	PCL-S	Not reported	6%	(+): Female gender, Barthel Index, Length of hospital stay (-): Age
(Sembi *et al.* 1998)	61	IES Penn CAPS	18 mos	21% 7% 10%	(+): Anxiety, Depression, Negative affect (n.s.): Gender, Age, Lesion location, pre-stroke medical or mental health problems, alcohol consumption, Time since stroke, Barthel Index

CAPS: Clinician Administered PTSD scale, IES: Impact of Event Scale, PCL-S: Post Traumatic Distress Scale, PDS: Post-Traumatic Distress Scale, Penn: Penn Inventory of PTSD
(+): Significant positive correlation $p<.05$, (-)Significant negative correlation $p<.05$, (n.s) No significant association

4.6 Discussion

This is the first known systematic review of anxiety prevalence after stroke. Anxiety disorders diagnosed by interview and anxiety symptoms assessed by rating scale occurred in 20-25% of patients at any time after stroke. Phobic disorders and GAD were the most common types of anxiety however this finding is based on data from only three studies. Similar prevalence has been observed in individuals other long-term conditions (Dissanayaka *et al.* 2010; Frasure-Smith and Lesperance 2008; Murphy *et al.* 2012), however the prevalence of anxiety amongst stroke survivors is higher than the 7% to 14% which has been observed in the general older adult population (Gum, King-Kallimanis and Kohn 2009; Ritchie, Artero and Beluche 2004)

The HADS was the most widely used rating scale for assessing anxiety symptoms. Validation of the HADS using different scoring thresholds has already been discussed in chapter two. However just to reiterate, the sensitivity for detecting anxiety disorders using the HADS-A in stroke patients using the 'probable' cut-off score of 10/11 ranges between 0.35 and 0.52 (O'Rourke *et al.* 1998; Sagen *et al.* 2009), and is only marginally better when using the lower 'possible 'score of 8/9. As a result the overall prevalence of anxiety 'caseness' could have been underestimated. On the other hand, the higher threshold has a higher degree of specificity, hence the proportion of individuals defined as anxious are more likely to represent genuine cases of significant anxious distress. The fact that there was such variability in cut-off scores likely contributed to the high levels of statistical heterogeneity observed in the pooled estimate of anxiety symptoms. However the alternative would have been to exclude a subset of studies which would be less than ideal. This highlights the need for further investigation into clinically relevant scoring thresholds that are appropriate for identifying individuals with substantial anxious distress who could benefit from some form of interventional support.

The prevalence of anxiety after stroke appears to increase somewhat over time, however the increase was not found to be statistically significant. It is possible that the lack of significance could be due to the stratified time-periods chosen *a priori*, however *post-hoc* analysis selecting different time-points did not show a significant increase over time either. With the exception of rates being lower in rehabilitation studies during the acute phase post

stroke, no other significant difference was observed based on the setting in which participants were recruited. A hypothesis is that the lower rate observed in the acute rehabilitation studies could be due to the structured supportive environment, or the notion that patients deemed appropriate for rehabilitation may be less disabled and less likely to be anxious. Given that anxiety prevalence beyond the acute phase is the same amongst rehabilitation patients as in other groups of patients, it is perhaps indicative of a negative shift in these patients' perception of their rehabilitation potential and chances of returning to their pre-stroke functional level.

There is insufficient information to determine whether the anxiety reported was a consequence of stroke, as the majority of studies only made cross-sectional assessments and did not consider the presence of pre-stroke anxiety levels in their assessments. Also, other factors that could impact the validity of prevalence estimates, such as medication use, the presence of cognitive or communication impairment, or previously having an anxiety disorder were not systematically investigated.

Despite having stratified analyses by study population and timing there was significant heterogeneity in the pooled estimates which impacts on the generalisability and interpretation of findings. Few studies differentiated between 'first-ever anxiety' and 'current anxiety' making it impossible to determine whether the differences in estimates represent genuine discrepancies or were due to measurement error or methodological differences. Second, the variation in type of stroke, stroke severity, and inconsistency of diagnostic tools and rating scales also contributed to the heterogeneity of the pooled estimate. The review relied on studies being catalogued in major search databases, however authors of studies whereby it was obvious that anxiety would have been assessed (e.g. HADS scale administered) were contacted for their anxiety data if it was not included in their publication. There was some evidence of possible publication bias in that small studies with larger standard error were found to yield higher prevalence estimates. It must be noted though that the relationship between sample size and prevalence is not causal. These studies may in fact have been drawn from populations that genuinely had higher levels of anxiety. Given the methodological variability in studies this is just as plausible an explanation. Additionally some studies were not included in the review as their data were unavailable and the influence this would have on the overall findings is unknown. With the

exception of the HADS and the BAI, the other scales used in these studies have not been validated in stroke populations, so their sensitivity and specificity are uncertain in this patient group. The HADS focuses on the psychic symptoms of anxiety and any physical indicators of anxiety not attributed to stroke have not been taken into account.

That none of the studies included in this review, included individuals with severe communication disorders, really underscores the need to develop anxiety assessment tools appropriate for this patient sub-group so they can begin to be included in future research. Other researchers have highlighted this as a research need (Kneebone and Lincoln 2012). To date a visual analogue mood scale found to be adequate in identifying depression post-stroke, has proved insufficient in screening for anxiety (Bennett and Lincoln 2006).

4.6.1 How does this review compare with other systematic reviews on psychological problems after stroke

A well conducted and frequently cited systematic review of 51 observational studies found that approximately 33% (95% CI 29-36) of individuals experience depression at some point after stroke (Hackett *et al.* 2005). This review will be referred to as the "Hackett review". Findings were stratified along the same time-periods and by the same method of case ascertainment as this review show that depression prevalence after stroke is higher:

- Depression [32%, 95% CI 19-44%] vs. anxiety [20%, 95% CI 13-26%] less than one month post stroke
- Depression [34%, 95% CI 20-39%] vs. anxiety [23%, 95%CI 19-27%] 1-5 months post-stroke
- Depression [34%, 95%CI 29-39%] vs. anxiety [24%, 95%CI 19-29%] six months or more post stroke

However, interpretation of this finding is difficult as it would be expected that a significant portion of individuals with depression also have anxiety and this is not taken into account in the depression prevalence studies. Additionally, unlike findings from the anxiety review, whereby anxiety prevalence was not higher amongst stroke survivors than in controls, the Oxfordshire Community Stroke Project study (House *et al.* 1991) found the frequency of depression was double that amongst stroke survivors than in matched population-based

controls. The trajectory of depression appears to differ as well. The Hackett review suggests that depression tends to resolve spontaneously within several months of onset in the majority of stroke survivors. The time course for anxiety in the few studies where it was assessed suggests it is more persistent in nature than depression. Depression co-morbid with anxiety was not reported in the Hackett review so no comparisons could be made. Lastly, because there was substantial methodological heterogeneity observed in both reviews makes the cross-comparison of findings challenging.

A systematic review of 20 studies on predictors of depression after stroke generated from the group of studies identified in the Hackett review was also carried out (Hackett and Anderson 2005). Age and gender were the two most commonly examined predictors of depression, as they were reported in 17 studies. Age was only associated with depression in four (24%) studies, and female gender in ten (58%) studies. Physical disability was investigated in 11 studies and was found to be associated with depression in nine (82%) of them. Having a personal history of depression was associated with depression after stroke in 5 of 8 studies. Additionally lesion location was not found to be significantly associated with depression as an association was observed in only 1 of 9 studies. However due to the paucity of well-designed studies with sufficient size to build stable multivariate models this review was only able to show that depression was correlated with certain factors.

No published systematic review was found on the prevalence of emotionalism after stroke, however it is estimated to affect between 20% and 25% of survivors in the first six months after stroke, and tends to decline in frequency and severity over the first year (Hackett *et al.* 2010). However even one year post-stroke up to 15% of survivors have been found to still be suffering with persistent and severe problems of emotionalism (Hackett *et al.* 2010). Stroke survivors describe feeling distressed and embarrassed, and thereby may engage in social avoidance or isolation which could impair overall quality of life (Hackett *et al.* 2010). This could potentially give rise to other mental health problems such as anxiety and depression.

4.6.2 Clinical and Research Implications

There is a high prevalence of reported psychological problems post-stroke. Taking into account that certain segments of the stroke population have not been included in the

review, the actual prevalence has likely been underestimated. Current guidelines for psychological care after stroke propose screening for anxiety within the first six weeks, however findings from this review show that anxiety was prevalent at time-periods well beyond six months. It is likely that stroke survivors would benefit from screening for anxiety throughout the entire rehabilitation pathway, and the presence of a more psychologically aware staff. Recent audits and surveys have found stroke survivors rated psychological services as unsatisfactory, and the ratio of psychologist to stroke patient population was well below the advocated minimum level, with some areas having very limited access to psychological support (National Audit Office 2010; McKevitt *et al.* 2011). Measures in place to improve access to psychological therapies and build psychological competency in non-specialist trained psychological or psychiatric staff will hopefully address the needs of stroke survivors.

Also of interest will be for future studies to examine the phenomena of anxiety and depression concurrently. The pervasive use of mood scales, such as the HADS, could facilitate an evaluation of the impact on patients with anxiety in addition to depression, as there could be differential risk factors and outcomes for those with anxiety only, depression only, and co-morbid anxiety and depression after stroke. However the design of most studies does not allow for any conclusion on this issue.

4.7 Summary

This review shows there has been a substantial number of studies that have assessed the frequency of anxiety disorders or symptoms after stroke. However information about timing of onset, risk factors and outcomes remains scant as investigating anxiety was rarely a primary objective of any of the included studies. Most studies tended to examine the phenomena of anxiety and depression in isolation. Given the variability in cut-off scores used in research studies, clear guidance on the appropriate point to screen for anxiety is needed, as this would reduce, at least marginally, the heterogeneity among future studies and provide more clarity for clinicians about treatment.

5 Chapter Five: Study 2- Cochrane systematic review of interventions used to treat anxiety after stroke

5.1 Introduction

The systematic review in chapter four quantified the extent to which anxiety after stroke is a problem. This chapter presents findings from a Cochrane systematic review on the effectiveness of interventions used to treat anxiety after stroke. Cochrane reviews are an international source of high quality, reliable health information that is readily disseminated to large audiences. These reviews facilitate choices that clinicians, patients, and policy makers face, and their structured easy to read format ensure that the information is appropriate for diverse audiences. The findings from this review have been published by the Cochrane Collaboration (Campbell Burton *et al.* 2011).

5.2 Rationale for review

Treatments for anxiety after stroke have received minimal attention both in clinical practice and research, relative to other post-stroke psychological conditions. Systematic reviews were previously carried out to assess the effectiveness of interventions used to treat depression and emotionalism when they occur after stroke (Hackett *et al.* 2008; Hackett *et al.* 2010). Despite there being a variety of treatment options available for anxiety, no equivalent systematic review had been conducted for anxiety post-stroke. Anxiety has been shown to increase the risk and severity of depression, and also has a negative influence on quality of life (Shimoda and Robinson 1998). Hence, treatment of anxiety could reduce the risk of subsequent depression and its associated adverse consequences, along with the unpleasant experience associated with anxiety.

5.3 Aim of review

The primary aim of this review was to assess the effectiveness of pharmaceutical, psychological, complementary or alternative therapy interventions in treating anxiety disorders or symptoms in stroke patients.

The secondary aim was to identify whether any of these interventions for anxiety had an effect on quality of life, disability, depression, social participation, caregiver burden or risk of death.

5.4 Methods

The following section describes the methods used to carry out this systematic review. Certain sections describe the specific contributions of the members of the review team and uses their initials. A glossary of names can be found in Appendix B.

5.4.1 Inclusion/ Exclusion Criteria

Randomised controlled trials (RCTs) where the primary aim of the intervention was to treat anxiety in individuals with a clinical diagnosis of stroke (Hatano 1976) were eligible for inclusion in this review. As there was no existing evidence base for treating anxiety after stroke, non-randomised studies were not included as they are more likely to provide biased information about the effectiveness of an intervention (Higgins and Green 2008). There was no restriction on the basis of language or study location. It was expected that eligible trials would compare the effect of an intervention plus usual care against placebo, a different intervention, or different doses or frequency of interventions. Trials had to have a placebo or standard care control arm otherwise they were not eligible for inclusion.

All stroke patients enrolled into a RCT had to have either a clinical diagnosis of an anxiety disorder according to the Diagnostic and Statistical Manual of Mental Disorders (e.g. DSM-III (American Psychiatry Association 1980),DSM-III-R (American Psychiatric Association 1987), DSM-IV (American Psychiatric Association 1994)) or similar diagnostic criteria. Stroke patients in RCTs deemed to have significant levels of anxiety symptoms as established by a pre-defined cut-off score on an anxiety screening tool as determined by the researcher(s), were also eligible. There were no restrictions on age distribution or gender. Studies with mixed populations of ischaemic or haemorrhagic stroke were eligible but studies assessing treatment effect in an exclusively subarachnoid haemorrhage patient population were excluded, as the characteristics, treatment, and management of these patients are substantially different to other stroke patients. Studies treating stroke patients for other conditions such as depression, cognitive impairment or physical disability were also

ineligible, unless it could be determined that all patients had co-morbid anxiety upon enrolment into the trial and treatment of the anxiety was one of the main objectives of the trial.

RCTs of pharmaceutical interventions administered to stroke patients compared with placebo or standard care were evaluated. The purpose of administering the drug had to be to treat anxiety. Trials where drugs were administered for other purposes such as neuro-protection were excluded. Trials of psychological interventions compared with placebo or standard care, which aimed to treat anxiety were eligible for inclusion. It was expected that these types of interventions would have a clearly defined psychological component, be structured, delivered and supervised by trained staff, and be time-limited. Interventions whose purpose was simply to provide information or educate patients were excluded. Trials such as occupational therapy or stroke support co-ordinator visitation were excluded unless they had a definitive psychological component aimed at treating anxiety.

5.4.2 Outcome measures

The primary outcomes of interest were:

1. the proportion of stroke patients without a clinical diagnosis of an anxiety disorder according to the DSM(American Psychiatric Association 1994) or another standard diagnostic classification system at the end of scheduled follow-up; OR
2. the proportion of stroke patients scoring outside the anxiety symptom range (as defined by study author); or the change score from baseline on an anxiety rating scale or via self-report at the end of scheduled follow-up.

The following secondary outcomes were also of interest.

1. Co-morbid depression, as diagnosed by DSM or determined by a depression rating scale such as the Beck Depression Inventory (BDI)(Beck, Ward and Mendelson 1961), or the Hamilton Depression scale (HAM-D) (Hamilton 1960).
2. Quality of life as measured on scales such as the 36-item short form questionnaire (SF-36) (Ware, Snow and Kosinski 1993).
3. Social activities as measured on scales such as the Frenchay Activities Index (Wade and Legh-Smith 1985).
4. Activities of daily living as measured on scales such as the Barthel Index (Mahoney and Barthel 1965).
5. Principal caregiver burden as measured by scales such as the Zarit Caregiver Burden Interview (Zarit, Rever and Bach-Peterson 1980).
6. Any adverse consequence as a result of treatment for anxiety such as drug tolerance, co-dependence on counsellor or death. We also recorded loss to follow-up rates in different arms of trials as a possible indicator of treatment acceptability.

5.4.3 Search strategy

The trials register of the Cochrane Stroke Group (October 2010), CENTRAL (The Cochrane Library 2010, Issue 4), MEDLINE (1950 to October 2010), EMBASE (1947 to October 2010), PsycINFO (1806 to October 2010), Allied and Complementary Medicine database (AMED) (1985 to October 2010), Cumulative Index to Nursing and Allied Health (CINAHL) (1982 to October 2010), Proquest Digital Dissertations (1861 to October 2010), and Psychological Database for Brain Impairment Treatment Efficacy (PsycBITE) (2004 to October 2010) were searched. See Appendix B for the search strategies used in various databases.

In attempt to identify additional published, unpublished, and ongoing trials the ClinicalTrials.gov (U.S. National Institutes of Health 2012), the Stroke Trials registry (The Internet Stroke Center 2012) and Current Controlled Trials (Springer Science+Business Media 2012) websites were also searched. Conference proceedings from the UK Stroke Forum (2006 to 2010), European Stroke Conference (2001 to 2010), and the International Stroke Conference (2007 to 2010) not already searched by the Cochrane Stroke Group Trials Search Co-ordinator were also reviewed. Science Citation Index Cited Reference search was used for forward tracking of relevant articles, and bibliographies of identified trials were reviewed. Experts known to members of the review team, or researchers with proficiency in psychological issues in stroke populations identified by scanning authors of relevant publications were contacted. The Association of British Pharmaceutical Industry, which includes the large majority of research-based pharmaceutical companies was contacted to request information about any relevant unpublished trials. However, there is compulsory registration of trials on public domain sites such as Clinicaltrials.gov and controlled-trials.com, therefore, making it unlikely that additional trials would be found.

The search did not exclude publications based on language. Translation was arranged for all potentially relevant non-English reports. For review of the search strategy see Appendix B.

5.4.4 Study selection and data extraction

For this part of the review, two reviewers (ACB and PK) independently screened all reports yielded from the searches of electronic databases, and excluded citations that were clearly irrelevant based on title and abstract. ACB retrieved the full text of the remaining articles and reviewed them for inclusion based on the eligibility criteria. If a consensus could not be reached between ACB and PK, a third member of the review group (DG) would have been consulted for adjudication. However, this was not necessary.

Two reviewers (ACB and JM) independently extracted data from included studies onto a paper extraction form where key information from studies was recorded. If information was missing, ACB attempted to contact the study authors, either by telephone or email, to request the missing data. Once the data extractions were reconciled, ACB entered them into Review Manager 5. The following core data elements such as details about the study design, methods, information about participants and outcomes for analysis were recorded. In the event that relevant data were missing, attempts were made to contact the study author.

5.4.5 Analysis

All the analysis for this review was carried out by ACB. Study bias was assessed in accordance with the Cochrane Collaboration's tool for assessing risk of bias (Higgins and Altman 2008). This instrument evaluates the sequence generation, allocation concealment, blinding (of participants, personnel and outcome assessors), incomplete outcome data, selective outcome reporting and other unspecified types of bias (e.g. conflict of interest). Biases from each study were summarised qualitatively and their potential impact on the findings were described. It was decided a priori that the longest time point post intervention initiation would be reported in the event the outcome was measured multiple times.

Several factors can contribute to the heterogeneity of studies and observed effect size. Subgroup analyses were planned on certain clinically relevant factors, such as specific type of anxiety disorder (e.g. GAD or social phobia), length of time treatment was administered, or length of time since stroke at entry into the trial. In order to assess the robustness of

findings, sensitivity analyses examining the degree to which they influenced the effect size were intended and would include studies whereby allocation concealment, double blinding, and fidelity to administered intervention were executed to the highest standard.

5.5 Results

5.5.1 Results of search

The search yielded 3486 unique titles Figure 5-1. Ten papers were retrieved for full text review. Additionally, 13 systematic reviews found in the search were reviewed for any possible additional citations. However, no new references were found using this method.

5.5.2 Included studies

Two trials with a total of 175 randomised participants met the inclusion criteria (Wang *et al.* 2005; Zhang, Zhang and Wang 2005). Table 5-1. shows a summary of the included studies. Neither trial had a placebo control arm, but compared the intervention group to standard care. Additionally both studies used the Hamilton Anxiety Scale (HAM-A) to evaluate the presence of anxiety (Hamilton 1969). The Hamilton Anxiety Scale is a rating scale developed to quantify the severity of anxiety symptoms, and is often used in psychotropic drug evaluation studies. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a five-point scale, ranging from zero (not present) to four (severe). Total scores on the HAM-A can range from 0 to 56. A score of 14 or more is suggestive of clinically significant anxiety.

5.5.2.1 Trial one (Wang 2005)

The first trial evaluated the effectiveness of the selective serotonin reuptake inhibitor (SSRI) paroxetine, and the combination of paroxetine and psychotherapy. Eighty-one first-ever stroke patients who met the Chinese Classification and Diagnostic Criteria of Mental Disorders (CCMD-3) criteria for anxiety and depression were randomised to one of the three groups. The first group (27 patients) received 20 mg of paroxetine per day, while the second group (27 patients) received the same amount of paroxetine per day along with psychiatrist administered supportive psychotherapy for 30 to 60 minutes once per week. A parallel control group with 27 patients received routine treatment only. The study authors

did not specify the length of time the participants were post-stroke at time of recruitment. Patients who were in a coma, aphasic, had severe cognitive dysfunction, other serious diseases or those who had been prescribed depression or antipsychotic medications in the three months prior to the onset of the trial were excluded. The interventions were carried out for six weeks and the HAM-A and the Hamilton Depression Scale (HAM-D) scales were used to assess the severity of anxiety and depression symptoms at baseline and at the two, four and six week time points during the treatment. Scores on the Barthel Index measuring activities of daily living were also assessed at all time points. Mean ages of participants were as follows: 62.4 years drug only group, 64.0 years in the drug plus psychotherapy group, and 63.2 years in the standard care group.

5.5.2.2 Trial two (Zhang 2005)

The second trial examined the effect of the anxiolytic drug buspirone hydrochloride against standard care. Ninety-four stroke patients with co-morbid anxiety and depression according to the CCMD-3 were recruited into the trial. Individuals with unstable conditions were deemed ineligible; however, no description of unstable conditions was provided. Buspirone was administered for four weeks to those in the intervention arm of the study. It was provided at 20 to 30 mg per dose during the first week, and then at 40 to 60 mg per dose during the second week. No information was provided about the amount administered during the third or fourth week. Anxiety and depression were measured using the HAM-A and the HAM-D scales at the baseline, and at two and four weeks during the intervention. The mean age of participants was 57.8 years for the intervention group, and 59.2 years for the control group. No other secondary outcome of interest was reported.

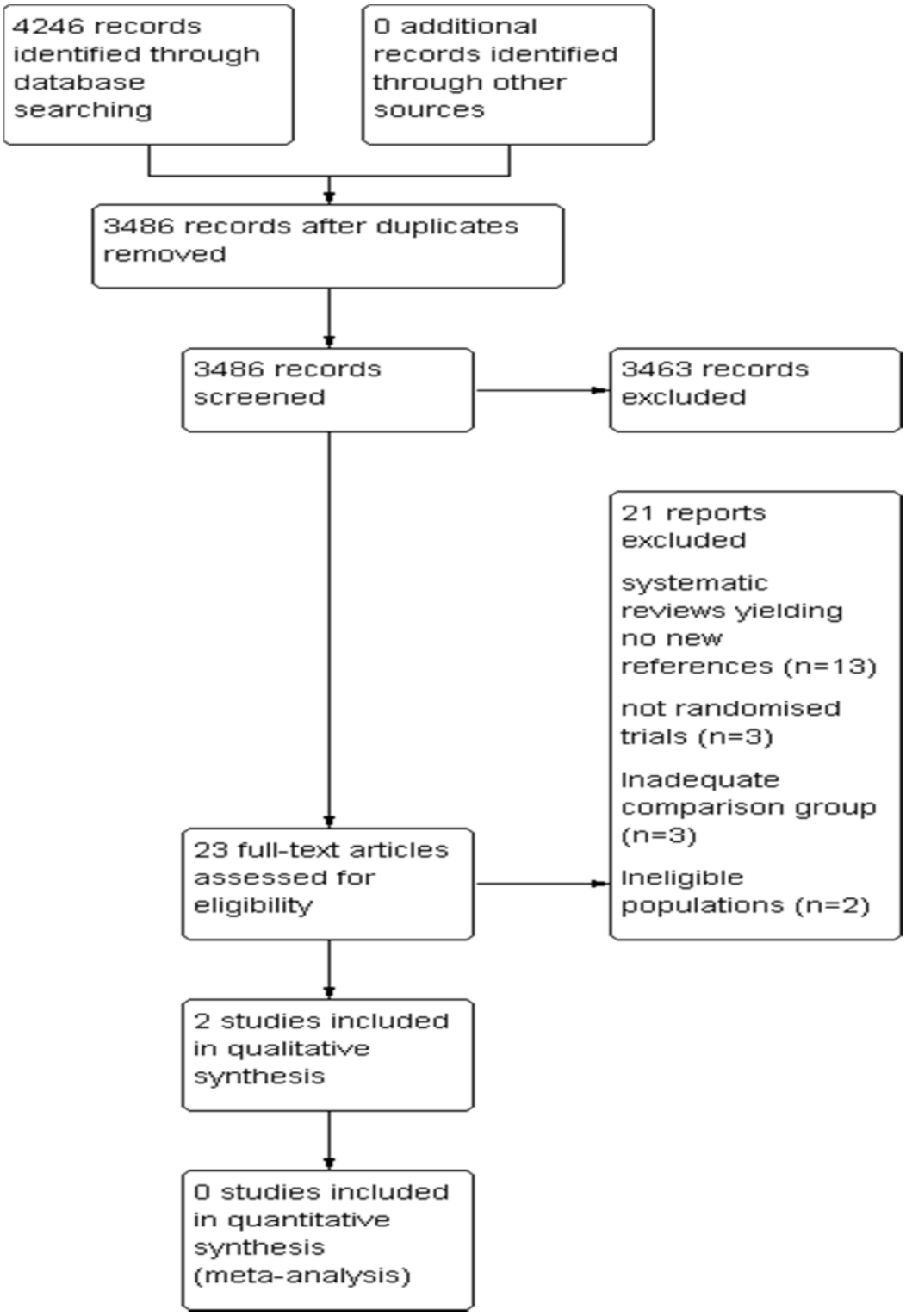


Figure 5-1 Search flow diagram

Table 5-1 Summary table of included studies

	(Wang *et al.* 2005)	(Zhang, Zhang and Wang 2005)
Location	China	China
Participants	81 first ever stroke with co-morbid anxiety & depression Group 1: n=27 Group 2: n=27 Group 3: n=27 52% male, 52% male, 52% male mean age 62 yrs mean age 64 yrs 63 yrs	94 patients with co-morbid anxiety & depression Group 1: n=47 Group 2: n=47 64% male, mean age 58 yrs 61% male, mean age 59 yrs
Interventions	Group 1: paroxetine 20mg daily + standard care Group 2: paroxetine 20mg daily+ psychiatrist administered individual supportive psychotherapy (30-60 mins)+ standard care Group 3: standard care only Duration: 6 weeks	Group 1: buspirone hydrochloride 20 to 30 mg daily in first week, 40 to 60 mg in second week + routine care Group 2: routine care (no description of routine care Duration: 4 weeks
Outcomes of Interest		
Anxiety	HAM-A: Mean score ± sd Group 1 Group 2 Group 3 Baseline: 14.0 ± 2.8 13.9 ± 2.9 13.8 ± 2.8 6 wks: 5.4 ± 1.7 3.8 ± 1.8 12.8 ± 1.9	HAM-A: Mean score ± sd Group 1 Group 2 Baseline: 22.7 ± 5.2 22.5 ± 4.3 4 wks: 6.5 ± 3.1 12.6 ± 3.4
Depression	HAM-D: Mean score ± sd Group 1 Group 2 Group 3 Baseline: 18.2 ± 1.4 18.8 ± 3. 18.0 ± 1.3 6 wks: 10.1 ± 1.1 8.9 ± 1.2 17.5 ± 1.1	HAM-D: Mean score ± sd Group 1 Group 2 Baseline: 24.6 ± 4.7 23.4 ± 5.3 4 wks: 8.3 ± 2.8 13.4 ± 2.7
Activities of Daily Living	Barthel Index: Mean score ± sd Group 1 Group 2 Group 3 Baseline: 60.9 ± 23.9 62.0 ± 23.1 61.5 ± 24.3 6 wks: 84.3 ± 8.4 90.2 ± 7.3 78.3 ± 15.0	Not measured
Notes:	*Exclusions*: coma, aphasia, severe cognitive dysfunction, other serious diseases, depression or antipsychotic medications within 3 months, allergic to paroxetine, or bipolar disorder	*Exclusion:* patients with unstable conditions

5.5.2.3 Intervention effectiveness

In the absence of any placebo-control group and because of generally poor description of the study processes, a meta-analysis was not conducted. The effectiveness of the interventions compared with standard care are described.

Trial one found that both paroxetine, and paroxetine plus psychotherapy reduced the severity of anxiety symptoms as measured by the HAM-A when compared with standard care. The mean HAM-A anxiety scores at baseline in the drug only, drug plus psychotherapy, and standard care groups were 14.0 ± (standard deviation (SD) = 2.8), 13.9 (SD =2.9) and 13.8 (SD = 2.8) respectively. At six weeks the mean anxiety scores were significantly lower in the two intervention groups relative to the controls 5.4 (SD = 1.7), 3.8 (SD = 1.8) in the drug only, and drug plus psychotherapy groups, but remained at 12.8 (SD = 1.9) in the control group. Relative to the standard care group, this represents a 58% and 71% lower mean anxiety score in the paroxetine, and paroxetine plus psychotherapy groups, respectively. These differences were statistically significant ($P < 0.01$). A similar trend was observed for mean depression scores as measured by the HAM-D. The possible range on the HAM-D is zero to 54, with higher scores indicative of more severe symptoms. Mean depression severity scores were 18.2 (SD = 1.4), 18.8 (SD = 3.1), and 18.0 (SD = 1.3) at baseline in the paroxetine, paroxetine plus psychotherapy, and standard care groups, respectively. While no change was observed in the control group after six weeks (mean 17.5, SD = 1.1), both the drug only and drug plus psychotherapy groups had significantly fewer depression symptoms (mean 10.1, SD = 1.1, and mean 8.9, SD = 1.2), respectively. This was also the only trial that reported changes in functional status as measured by the Barthel Index of activities of daily living (ADL). It found that ADL improved significantly in all three groups of patients but the greatest improvement was observed in the drug plus psychotherapy group, followed by the drug only group, with the standard care controls having the least improvement.

Trial two found that buspirone hydrocholoride was effective in reducing anxiety symptoms when compared with standard care. Four weeks after drug initiation the mean anxiety score on the HAM-A decreased from 22.7 (SD = 5.2) to 6.5 (SD = 3.1) in the intervention group. This was a significantly larger decrease than seen in the standard care

group (P <0.01) where the mean anxiety score decreased from 22.5 (SD = 4.3) to 12.6 (SD = 3.4) after four weeks. The mean in the intervention group was 50% lower than those receiving standard care only. Buspirone was also effective in significantly reducing depression symptoms as measured on the HAM-D in the intervention group compared with the controls. The mean depression score in the intervention group decreased from 24.6 (SD = 4.7) to 8.3 (SD = 2.8) and from 23.4 (SD = 5.3) to 13.4 (SD = 2.7) in the standard care group.

5.5.2.4 Adverse events

No participants were lost to follow-up in the Wang et al trial. However, in Zhang (2005) trial, both the intervention and control groups lost 23% of their participants. Reasons given for drop out in the intervention group were unsatisfactory treatment effect, drug side effects, and subsequent prescription of benzodiazepines. Recurrent stroke, having benzodiazepines prescribed, and withdrawal were reasons given for loss to follow-up in the control group.

5.5.2.5 Bias in included studies

Cochrane systematic reviews consider several risk of bias indices that may influence heterogeneity of study results. Selection bias refers to systematic differences between baseline characteristics of the groups being compared. It is based on two concepts: a) sequence generation, a specified rule for allocating interventions to participants which should be based on some type of chance or random process, and b) allocation concealment, which is a system that prevents foreknowledge of forthcoming allocations. Wang et al (2005) stated that they used simple random sampling, and Zhang (2005) indicated that they used a random number list for participants who met the inclusion criteria, however the randomisation process was not described in either study.

Blinding is the procedure that prevents study participants, caregivers, or outcome assessors from knowing which trial arm a participant has been allocated to. Neither study provided information about blinding, and as there was no placebo control group blinding would likely only be possible for independent outcome assessors, and there was no indication that any were involved in these trials.

Attrition occurred in the Zhang (2005) trial only and available case analysis was carried out in this study. There was no indication that participants in the Wang et al (2005) study did not adhere to treatment protocol. Additionally, there was no evidence of selective outcome reporting in either of the trials. All outcomes measured and reported in the methods of both studies at the onset of the trial were reported for all time points. However, the research protocols were not available, so it is unknown whether other outcomes were measured but not reported.

5.5.3 Excluded studies

Eight studies were excluded from the review. Three studies (Liu, Liu and Liang 2004; Ye *et al.* 2006; Wu and Liu 2008), had no adequate control group (i.e. no placebo or standard care). In four studies anxiety levels of the participants were assessed but did not meet a pre-defined threshold definition so it could not be established that all participants had anxiety upon entry into the trial (Morrison *et al.* 1998; Mok and Pang 2004; Li 2005; Rorsman and Johansson 2006). In addition three studies (Morrison *et al.* 1998; Kimura, Tateno and Robinson 2003; Li 2005) were not randomised control trials. One study (Morrison *et al.* 1998), was a quasi-experimental cohort study design using retrospective controls, and in another study participants acted as their own controls. The criteria for entry into one study (Kimura, Tateno and Robinson 2003) was depression, and a subset analysis on cases with co-morbid depression and GAD was conducted. A summary table of the excluded studies can be found in Appendix B.

5.6 Discussion

5.6.1 Completeness and Applicability of evidence

The scope of this review was deliberately broad as it was suspected the completed research on interventions used to treat anxiety after stroke was not as established as some other post-stroke psychological conditions. Very little information was provided about the populations from which the participants were selected, hence the findings of this review may not even be generalisable to the stroke population from which they were drawn let alone stroke populations in other locales. Another concern was that the inclusion criteria for both studies required participants to have co-morbid anxiety and depression according

to the CCMD-3. This would result in stroke patients with anxiety only being ineligible for inclusion into the trial. As a result there is no evidence as to whether any of the interventions described would be effective for stroke patients who only had anxiety and not depression. It should be noted that while the HAM-A is widely used in pharmaceutical studies of anxiety, it is not appropriate as a diagnostic or screening instrument. The HAM-A focuses primarily on the phobic and autonomic arousal symptoms of anxiety, and gives little weight to the psychological symptoms. Given the physical consequences of stroke, it would be misleading to attribute all physical symptoms solely to anxiety.

5.6.2 Quality of the evidence

Clear conclusions about the evidence cannot be drawn as many of the quality indices were not adequately described, and study sample size was small in both included trials. No study provided information on the length of time that had passed between stroke and participant enrolment into the trial and no information was provided about the setting from which participants were recruited (e.g. hospital, or community based). This could influence prevalence of anxiety as patients in hospital or rehabilitation settings may have different levels of mood disturbance. Another issue is that neither study described what was involved in the routine or standard care groups which were used as the control comparison. Lastly, all studies inadequately reported their methodological indices such as allocation concealment or blinding of participants and outcome assessors.

5.6.3 Potential biases in the review process

To the extent possible, there was minimal bias in the review process. An extensive literature search guided by the Cochrane Stroke Group methodology was carried out, and key researchers in the field were contacted to obtain information about studies with a focus on post-stroke anxiety. Additionally, the findings were not limited to English-only papers. Two individuals independently decided whether studies should be included and data were extracted independently by two review authors.

5.6.4 Implications for clinical practice and research

Currently there is insufficient evidence to guide practice in treating anxiety after stroke. The pharmaceutical therapies evaluated indicate that medication may be an

effective approach for reducing anxiety symptoms in stroke patients with co-morbid anxiety and depression when compared with standard care. The clinical significance of this decrease is unclear as the authors did not provide any information about the proportion of study participants no longer meeting the anxiety criteria. However, research has indicated that a reduction of more than 50% on the Hamilton Anxiety Scale is indicative of obvious improvement in the level of anxiety (Ye *et al.* 2006).

Given the high prevalence of anxiety after stroke, placebo controlled trials are needed to identify effective treatments for this condition, as it can have a negative impact on other aspects of life. Future research evaluating interventions to treat poststroke anxiety should assess outcomes such as quality of life and caregiver burden as the trials in this review provided no information on these outcomes. Additionally, researchers should ensure that patients with anxiety only are also recruited into trials. Lastly given there is moderate, albeit non-significant advantage for some psychological therapies in treating anxiety versus depression (Roshanaei-Moghaddam *et al.* 2011), a trial investigating the effectiveness of psychological interventions would be useful for informing clinicians. This would also be in keeping with current guidelines that recommend that the option of psychological therapy be available for patients.

5.7 How does this review compare with other Cochrane reviews on psychological problems that occur after stroke

5.7.1 Cochrane review for treating depression after stroke

It would be difficult to conduct a review on anxiety after stroke without discussing interventions used to treat depression after stroke, given the two conditions are so closely linked. A Cochrane systematic review of 12 randomised control trials (13 interventions) of pharmaceutical therapy in 1121 stroke patients with depression found that overall there was some evidence of significant benefit for drug therapy in treating depression (i.e. remission of symptoms) after stroke (Hackett *et al.* 2008).

Seven of these studies looked at the effect of selective serotonin reuptake inhibitors (SSRIs), two evaluated tricyclic antidepressants (TCA s) and the remainder looked at other individual antidepressant drugs which included deanxit, aniracetam, reboxetine and

trazodone. There was evidence of significant adverse events associated with drug therapy, as increased incidence of central nervous system problems such as confusion, sedation or tremors and gastrointestinal effects in intervention group relative to the controls was observed. In terms of other outcomes assessed in this review there was no evidence of benefit in terms of cognitive functioning, activities of daily living, or improvement in neurological functioning.

Unlike the anxiety review, the depression review (Hackett *et al.* 2008) found four psychologically based therapies in 445 stroke participants with depression. The following interventions had been administered: Motivational interviewing delivered by nurses and non-clinical psychologists, cognitive behavioural therapy (CBT); problem-solving therapy with counselling delivered by social workers; and a supportive psychological therapy with education delivered by special personnel. None of these trials demonstrated any evidence of benefit (albeit motivational interviewing showed some trend favouring the intervention that failed to meet clinical significance) in terms of treating or reducing depression symptoms. Neither were they effective in reducing psychological distress or improving activities of daily living. It should be noted that in the systematic review, motivational interviewing included findings only from depressed individuals recruited into the trial, of which there were significantly less in the intervention group relative to the control. This discrepancy between the two groups likely explains why the intervention was not found to be effective, when it was found to be effective in significantly reducing depression in the overall study population. However unlike the drug therapy trials the incidence of adverse events was not higher in the intervention groups. Additionally there was less (although non-significant) loss-to follow-up in the intervention groups relative to the control, perhaps indicating increased treatment tolerance.

There was substantial heterogeneity between studies, hence the findings from this review should be interpreted with caution. Study populations were extremely mixed. For example there was large disparity in timing of recruitment into trials of patients ranging from several days to more than two years post stroke. Additionally the criteria for enrolment were quite restrictive in several trials in that patients with communication problems, cognitive loss, or previous psychological illness were ineligible to participate.

These types of exclusions affect the generalisability of findings, as clinically it is impossible to preclude these types of patients from presenting in clinic.

The last criticism is that of trial methodology itself. While psychologically based interventions were not found to be effective for treating depression after stroke, one needs to consider that generally those receiving psychological care tend to be referred from primary or community care services. It is possible that individuals referred to psychological care would chose to engage more with treatment, as opposed to individuals within a trial who are simply randomly assigned to an arm of a trial, and for whom treatment preference has not be taken into account.

5.7.2 Integrating post-stroke anxiety and depression intervention findings

In comparison to the review on anxiety, the body of evidence for pharmaceutical effectiveness in treating depression after stroke is greater. With the exception of one trial that used aniracetam, (a drug that at the time of writing this thesis is not currently recommended for treating anxiety in the UK), presence of co-morbid anxiety presence was not assessed. So while there is significant overlap in appropriate interventions that can be used to treat anxiety and depression, findings from the depression review should be interpreted with caution when dealing with anxiety, because there are etiological and phenomenological differences between the two conditions, and successful treatment of depression would not necessarily result in resolution of anxiety in instances of co-morbidity.

5.7.3 Reviews of other interventions

There have been few reviews examining the effectiveness of interventions on psychological outcomes after stroke. No interventions thus far have shown to be effective in reducing anxiety levels. A systematic review on information provision after stroke found some statistically significant but clinically small benefit in reducing anxiety levels (Smith *et al.* 2008). However systematic reviews looking at physical fitness (Saunders *et al.* 2009), speech language therapy (Kelly, Brady and Enderby 2010), and the use of stroke liaison workers (Ellis *et al.* 2010), all found none of these interventions were effective in reducing anxiety. One of the main criticisms of these reviews is that there is significant heterogeneity amongst the interventions evaluated, and many interventions used in trials have been

atheoretical in their approach. Hence more consideration should be given to how an intervention may work prior to investigating whether it works. This may increase the likelihood of identifying effectiveness, as there would be a greater understanding of the underlying mechanisms of the intervention which then could inform study design and outcome assessment.

5.8 Conclusion

Currently there is insufficient evidence from randomised trials to guide practice in treating anxiety after stroke. The pharmaceutical therapies evaluated indicate that drugs may be an effective approach for reducing anxiety symptoms in stroke patients with co-morbid anxiety and depression when compared with standard care. The clinical significance of this decrease is unclear as the authors did not provide any information about the proportion of study participants no longer meeting the anxiety criteria. However, research has indicated that a reduction of more than 50% on the Hamilton Anxiety Scale is indicative of clinically significant improvement in the level of anxiety (Ye *et al.* 2006). Additional research is warranted in this area. However, while it is sufficient to say that additional trials are required, investigation into the theoretical constructs that may serve as determinants of an interventions failure or success is also needed. For example, anxiety is viewed as being more amenable to being treated with a psychological intervention, whereas depression is seen to have more of a biological aetiology and more likely to benefit from drug therapy (Edwards *et al.* 2007; Prins *et al.* 2008). This link between anxiety and psychology is what led to the investigation of illness representations and their possible association with anxiety after stroke. The methods and results of that work are described in the following chapters.

6 Chapter Six: Study 3- Methods

6.1 Introduction

This chapter describes the methods used in the empirical study of this thesis. It provides a rationale for and description of the study design. The main tools used to assess anxiety symptoms, illness representations, and functional impairment are described. The final section provides detail of the statistical approach used to describe the study population along with the regression analysis and structural equation modelling techniques employed for the predictive analyses.

6.2 Purpose of Study

The research surrounding illness representations and psychological outcomes within the stroke population have been largely limited to cross-sectional studies (Ford 2007). While such studies are useful for establishing association, they do not allow for inference of a temporal relationship between constructs. When a longitudinal approach has been employed, anxiety has not been a primary outcome of interest, or the researchers have not used the Leventhal Common Sense Model (CSM) of illness representations (Twiddy, House and Jones 2012; Morrison, Johnston and Mac Walter 2000). There is a paucity of longitudinal data assessing the course of anxiety after stroke, and its predictors. Understanding the illness representations held by stroke survivors will shed light on whether illness representations are associated with psychological outcome after stroke, and could prove useful for clinicians in helping them develop interventions tailored at treating anxiety after stroke.

6.3 Primary Research Aims

1. To assess and compare the prevalence and severity of anxiety at two time-points after stroke.
2. To assess illness representations and changes in illness representations in stroke patients.
3. To determine whether illness representations and/or clinical factors, are associated with anxiety after stroke.

4. To assess whether illness representations and/or clinical factors are predictive of anxiety at follow-up after stroke.

6.4 Design

A prospective, longitudinal, repeated measures design was used to assess anxiety (and depression) symptoms, illness representations, and functional impairment in activities of daily living. Measurements were obtained at baseline (time 1), which ranged from less than one month to six months post-stroke. A follow-up assessment (time 2) was obtained three months after the baseline assessment. The main advantage of a longitudinal design is that both change and predictors of change over time can be assessed.

6.5 Setting

6.5.1 Barnsley Hospital NHS Foundation Trust

Barnsley Hospital NHS Foundation Trust is located in the South Yorkshire region of England and was the main site for patient recruitment. Approximately 224,000 people reside in Barnsley and it has traditionally been an area with little ethnic diversity as approximately 98% are white British (Barnsley Council). There are close to 400 new strokes in Barnsley each year and about 5000 individuals living with some form of stroke related residual disability (Barnsley Hospital NHS Foundation Trust). The outpatient stroke clinic where recruitment occurred is integrated with other stroke services in the area and the majority of stroke patients will have at least one follow-up visit after discharge from the hospital stroke unit, inpatient rehabilitation, or early supported discharge (Figure 6-1). Table 6-1 provides a description of the study sites.

This clinic conducts follow-up appointments with the majority of stroke and TIA patients in the region after they have been discharged into the community from either the acute stroke unit, or inpatient rehabilitation. Patients receiving early supported discharge (ESD) and those referred by their GP with suspected TIA are also seen in the outpatient clinic. Prior to study commencement, it was estimated that the outpatient clinic saw approximately 50 stroke patients per month (personal communication). Stroke patients residing within the Barnsley catchment area are generally seen at this clinic approximately six weeks after discharge from the stroke unit. Patients who are not admitted to the stroke

unit or do not present to hospital at the time of stroke (i.e. minor TIAs) also receive follow-up appointments to the outpatient stroke clinic. Clinics were held on two afternoons per week. One of the clinic days received a varied case-mix of patients with long-term conditions (e.g. Parkinson's disease), while the other saw exclusively stroke patients. The stroke clinic was led by either a stroke consultant or stroke nurse specialist. On a few occasions, when neither the consultant nor the nurse were available, a medical registrar was responsible for seeing patients at their appointment.

6.5.2 Sheffield Teaching Hospital NHS Foundation Trust

Within the first few weeks of recruitment at the Barnsley site it became apparent that it would be difficult to recruit a sufficient sample within the six months timeline specified in the project work-plan. As a result it was decided to expand the research site to Sheffield. Sheffield is located in South Yorkshire and is one of the largest cities in England with a population of 555,000 (Sheffield Director of Public Health Report 2008). Hospital based stroke appointments are provided at two teaching hospitals (Intercollegiate Stroke Working Party 2010). It is more ethnically diverse with approximately 10% of the population self-identifying as belonging to a minority ethnic group. Each year in Sheffield about 1150 individuals have a stroke and another 500 have a TIA (Sheffield Director of Public Health Report 2008). Generally speaking the overall pattern of patient referral is similar to that described in Barnsley. There were several outpatient follow-up clinics for stroke patients each week, however many of them were attended by patients with other long-term conditions (e.g. Parkinson's disease, dementia). Recruitment occurred from one outpatient clinic that ran weekly and saw exclusively with stroke patients.

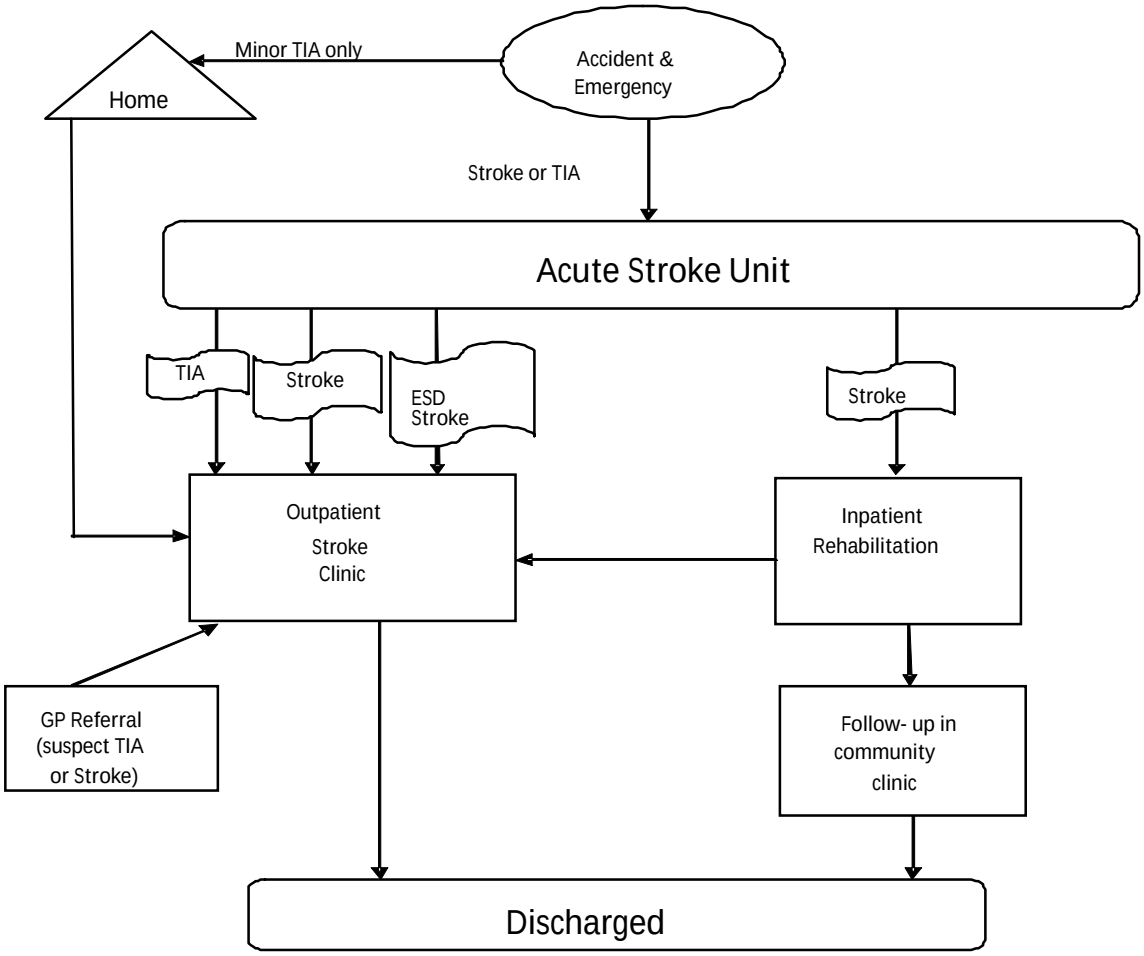


Figure 6-1 Integrated stroke care pathway

Table 6-1 Description of Study sites

	Barnsley	Sheffield
Total population	224,000	550,000
% Ethnic Minority	1	9.5
No. of Stroke & TIA per years	400	1600
No. of beds used for pre-post 72 hours stroke care	19	22
No. beds for post 72 hour stroke care only	24	64
Availability of Specialist Early Supported Discharge teams	YES	YES
Availability of Long-term specialist community rehabilitation teams	NO	NO

Source: National Sentinel Stroke Audit 2011,

6.6 Measures included in the questionnaire package

The following section describes the measures and the rationale for their inclusion in the participant questionnaire package (Appendix C). Information about reliability and validity is also provided.

6.6.1 Assessing anxiety: The Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) is a self-report questionnaire consisting of seven anxiety and seven depression items which form two separate subscales. Scores on each subscale range from 0-21, with higher scores reflecting greater levels of anxiety or depression. Patients choose one of four answers to each question, indicating how they have been feeling in the *past week*. Originally designed for use in hospital patients, it was developed to overcome two common problems of assessment in this group; the first being to circumvent confounding of symptoms of physical illness and mood disorder, and the second to develop a short, easy to use tool that distinguishes anxiety and depression, and is not simply a general measure of psychiatric distress. As a result the HADS asks only about psychological symptoms of anxiety such as worry, restlessness, and feelings of panic and reduces the possibility of inflated anxiety prevalence estimate based on attributing the physical symptoms of stroke to anxiety. Its intended use was as a screening measure to detect clinical cases of anxiety and depression. As highlighted in chapter two, there are different underlying assumptions of diagnostic and symptom rating severity metrics, however both of these functions are often given the same term, "anxiety". The term anxiety as applied to the results of this empirical study refers to symptom severity and not diagnosis.

6.6.1.1 Rationale for using the HADS

The criteria used for selecting an anxiety rating scale in this study were that the scale would measure both anxiety and depression, have simple response categories for participants to select, and would not be excessive in length. Additionally when selecting screening tools for assessing mood, Bennett et al (2006) argued that it is important that the rating scale is both sensitive and specific and that the optimum cut-offs are known for stroke patients rather than just in the general population (Bennett *et al.* 2006). The review

of assessment scales in chapter two showed that the HADS is the only validated scale meeting these criteria.

The psychometric properties of the HADS when measuring both anxiety and depression have been validated in the stroke population (Chapter 2). Additionally as observed in the systematic review on the prevalence of anxiety after stroke (Chapter 4), the HADS is the most widely used anxiety screening measure in stroke, and with its short administration time (<5 minutes), is generally well accepted by patients (Herrmann 1997). Relative to other commonly used mood scales it is easier to use in stroke patients (O'Rourke *et al.* 1998). It was also thought that the use of the HADS would allow for comparison between this study and the existing published literature such as those studies included in the prevalence systematic review.

6.6.1.2 Reliability of the HADS

Reliability testing has shown satisfactory or good item-total correlations within both the anxiety and depression subscales, and good internal consistencies ranging from 0.80-0.93 on both subscales (Herrmann 1997). Retest reliability findings show a high correlation, ($r>0.80$ after two weeks), which decreases to about 0.70 with longer intervals of time (Herrmann 1997). Hence unlike many instruments that measure mood state, the HADS is stable enough to withstand situational influences on mood scores. Additionally, the two factor model of anxiety and depression assessed in the HADS has been consistently supported (Herrmann 1997). While the anxiety and depression sub-scales often correlate very highly, this is likely due to the real coincidence of anxious and depressed symptoms found in many patients, rather than being an inadequacy of the instrument.

6.6.1.3 HADS validity and scoring

An issue that confounds the use of symptom rating scales is that some anxiety disorders involve persistent symptoms of anxiety, such as General Anxiety Disorder (GAD) or post –traumatic stress disorder (PTSD), whereas other disorders are episodic or situational, such as specific or social phobia. Hence using the same scale to rate anxiety symptoms that are episodic as opposed to persistent is problematic. In any case Zigmond and Snaith (1983) advise that a score of 8 or more is indicative of a possible anxiety disorder, and 11 or more

as a probable disorder. Within the field of stroke, it has been proposed that anxiety rating scales should have a sensitivity of ≥0.80 and specificity of ≥0.6 (Bennett and Lincoln 2006).

Two studies, (O'Rourke *et al.* 1998; Sagen *et al.* 2009) validated the HADS anxiety subscale against the DSM-IV criteria for anxiety. From their findings they recommend using HADS-A cut-off scores that range from 4 to 7. At these levels sensitivity ranged from 0.78-0.83, and specificity ranged from 0.65-0.72. Despite the findings from the validation studies the rationale for the above mentioned sensitivity/ specificity threshold suggestions has not been provided. Additionally, the overview of validation studies described in chapter two highlights the risk of increased misclassification when lower HADS-A threshold scores are used.

The evidence to abandon the scoring criteria proposed by scale authors is inadequate. Findings from the prevalence review of anxiety after stroke (chapter 4) in which a lower HADS-anxiety subscale threshold was used in some studies did not yield results that were substantially different from the ones prescribed by the scale authors. An anxiety case in the empirical research of this thesis was defined as having a score of >=11 on the anxiety subscale of the HADS which is in keeping with the guidance of Zigmond and Snaith (1983). Use of the higher threshold increases the positive predictive value of the scale. An endorsement of as few as two questions on the anxiety subscale could result in labelling an individual as anxious, were a lower threshold applied. The use of the prescribed anxiety criteria meant that findings obtained in this study could be placed in context with the extensive body of literature already available that used the recommended cut-offs. Even though a conservative approach to defining an anxiety case has been used, it is acknowledged that an individual could have a very low score but still feel tremendously anxious. Likewise a high score is not necessarily indicative of an anxiety disorder.

6.6.1.4 Licensing

A research license for the HADS was obtained from GL Assessment. The qualification and access-code are attached in (Appendix D).

6.6.2 Assessing Illness Representations: The Revised Illness Perception Questionnaire (IPQ-R)

The conceptualisation of illness representation has its roots in fear communication studies. Leventhal's original work sought to understand the illness experience by conducting a series of in-depth semi-structured interviews. From this it was found that several constructs were consistently observed across a wide range of conditions (Leventhal, Nerenz and Steel 1984; Savage and Clarke 1998). However while in-depth interviews can yield valuable information, they are time consuming and it is difficult to compare findings between studies.

The Illness Perception Questionnaire (IPQ)(Weinman *et al.* 1996) was the first attempt to systematically assess the core cognitive facets of illness representations and was developed across several illness groups (Weinman *et al.* 1996). The IPQ, consisted of five cognitive components (identity, consequences, timeline, control/cure, and cause) of individual illness representations. While the establishment of the IPQ encouraged additional research in the area of self-regulation and health, problems with the internal consistency of the control and timeline subscales became apparent (Moss-Morris *et al.* 2002). Additionally it lacked capacity to fully describe the illness response, as it did not include emotional representations, which are an important concept in the Leventhal self-regulatory model.

The Illness Perception Questionnaire (IPQ-R)(Moss-Morris *et al.* 2002) was subsequently developed to address the limitations of its predecessor the IPQ. New symptoms were added to the core identity subscale list. Patients are asked if they had experienced a set of symptoms since the onset of their disease or condition, and if so whether they attribute these symptoms to their illness (i.e. the stroke). The scale authors encourage the addition of other symptoms to the core identity list of 14 items that may be related to the disease of interest. The identity subscale score comprises the sum of the attributed stroke symptoms. Evaluating the symptoms 'attributed' to stroke rather than symptoms 'experienced' avoids potential somatisation of symptoms and instead taps into the concept of illness identity (Moss-Morris *et al.* 2002). The IPQ-R was also extended to include measures of illness coherence and emotional representation of illness, and there

were improvements in the reliability and validity of the timeline domain. In the IPQ-R the acute/chronic component of illness representation is separated from cyclical timeline aspects that may be associated with certain conditions. The addition of the cyclical timeline domain is particularly relevant for investigation into diseases such as stroke which may, or may not be captured on a simple acute/chronic dimension. Care was also taken to ensure that the emotional representation scale was not just a reflection of affective disposition. However, there is some overlap between negative affect and the emotional representation sub-scale, in that negative affect accounts for approximately 29% of the variance in the emotional upset generated by the illness. Causal items were extended from 10 to 18, and exploratory factor analysis can be conducted to establish underlying causal factors where sample size is sufficient. Excluding the identity and causal sections, the IPQ-R consists of 38 items which generate seven illness domains that accounted for 64% of the variance in its test population of 711 individuals from eight different illness groups (Moss-Morris *et al.* 2002).

6.6.2.1 Rationale for using the IPQ-R

The illness representation hypothesis uses a common sense approach to explaining the phenomenon of ill health. However the underlying concepts that can interpret or explain health behaviour or perception are complex and multilevel. Several questionnaires have been developed to assess illness representations (Partridge and Johnston 1989; Evers *et al.* 2001; Browne *et al.* 1988), however they were not designed for the purpose of measuring the domains defined by Leventhal. As such the IPQ-R is currently the best available tool for investigation into the phenomenon of illness representations. The IPQ and IPQ-R are also the most popular questionnaires used to assess illness representations (Hagger and Orbell 2003).

6.6.2.2 IPQ-R Domains

The illness identity scale is the first domain on the IPQ-R. In line with previous research (Twiddy 2008) the version used in this study contained an additional 10 items not part of the author derived core list. The identity domain shows the label ascribed to an illness and concrete signs and symptoms ascribed to the condition. The appraisal of

perceived symptoms is an important cue to guide health behaviours, such as adherence to treatment, self-diagnosis or help-seeking behaviours.

The remaining seven domains are:

1. Timeline (acute/chronic)- evaluates perceptions of the likelihood that the condition will be chronic in nature
2. Consequences- deals with beliefs about illness severity and its impact on physical, social, and psychological functioning
3. Personal control- assesses beliefs about personal control over the illness
4. Treatment control- assesses beliefs about whether the illness can be cured through treatment
5. Coherence- gauges how much an individual understands or comprehends their illness
6. Timeline (cyclical)- evaluates the perceptions of the likelihood that symptoms associated with the condition will vary over time
7. Emotional- deals with the perception of negative emotions and feelings arising as a result of the condition

6.6.2.3 Scoring the IPQ-R

With the exception of the identity scores, the domains of the IPQ-R are scored on a five point Likert scale ranging from 'strongly agree' to 'strongly disagree'. High scores on the timeline, consequences, and cyclical dimensions reflect strongly held beliefs about the chronicity and negative consequences of the condition, or indicate strongly held beliefs that the condition is cyclical in nature. Higher scores on the personal control, treatment control, and coherence sub-scales reflect strongly held beliefs that the illness is controllable with either personal effort or treatment, and that the respondent has a greater personal understanding of their condition. High scores on the emotional domain indicate that the condition has significant negative emotional consequences.

The scale authors have developed a website with instructions for scoring the IPQ-R (http://www.uib.no/ipq/). Illness identity is calculated by summing the 'yes' responses to the experience of symptom attributed to stroke. Responses on the other sub-scales are

scored accordingly ('strongly disagree'= 1,'disagree'= 2, 'neither agree nor disagree' =3, 'agree' =4, 'strongly agree' =5). As per author instruction, items IP1, IP4, IP8, IP15, IP17, IP18, IP19, IP23, IP24, IP25, IP26, IP27, and IP36 are reverse coded (1=5, 2=4, 4=2, and 5=1). The respective subscales are calculated by summing the following items:

1. Timeline (acute/ chronic): IP1- IP5 + IP18
2. Consequences: IP6-IP11
3. Personal Control: IP12-IP17
4. Treatment control: IP19-IP23
5. Illness coherence: IP24-IP28
6. Timeline (cyclical): IP29-IP32
7. Emotional Representations: IP33-IP38

Authors indicate that for subscales with six items, a maximum of 2 missing items are allowed. One missing item is allowed for each of the remaining subscales.

6.6.2.4 Reliability and validity of the IPQ-R

Perhaps, because of the novelty of the scale, test-retest reliability of the IPQ-R has not been studied extensively. Moss-Morris et al (Moss-Morris *et al.* 2002) assessed it within a subset of rheumatoid arthritis patients and found good stability over three weeks with correlations ranging from 0.60 to .88 for all domains, except personal control which was lower at .46. The stability of representations was somewhat lower when measured over six months but all were still relatively high with all correlations over 0.5. Reliability testing carried out in a small convenience sample of stroke patients found correlations ranging between 0.6 and 0.8 over two months (Twiddy 2008). Unlike conditions where a definitive diagnosis is necessary for classifications, illness representations are likely to fluctuate with time.

Selecting a criterion upon which to validate the IPQ-R is challenging as its aim is to measure a theoretical construct. However, discriminant validity testing conducted to determine whether the IPQ-R domains were not simply a reflection of positive or negative affect, were for the most part non-significant (Moss-Morris *et al.* 2002). However, the emotional and consequential representations did show some association with affect.

6.6.3 Assessing Impairment in Activities of Daily Living: The Barthel Index (BI)

The Barthel Index (BI) is a 10 item scale used extensively within rehabilitation and stroke populations (Quinn, Langhorne and Stott 2011). It was developed to measure a person's daily functioning ability, specifically the activities of daily living (ADL) and mobility. The items include feeding, mobility, grooming, toileting bathing, walking, and continence. Its aim is to assess what a person *actually* does rather than what they *can* do. The original version used a rating system whereby patients received a score ranging between 0 and 100, with lower scores representing greater dependency (Mahoney and Barthel 1965). Individual questions were given weighting scores between 5 and 15.

A modified version of the BI used in this study (Gompertz, Pound and Ebrahim 1994) asks the same 10 questions found in the original version with a simplified weighting scheme and total possible scores ranging from 0-20. Lower scores are indicative of higher levels of dependence. As the 100 point and 20 point versions are equivalent in content, the change in scoring does not have an effect on the clinimetrics. There is no general consensus on how scores should be interpreted, however one suggestion is that a score <4 indicates total dependence, 5-11 some dependence, and ≥12 independence (Gupta 2008).

The BI is not a continuous scale and a one point change at the top of the scale does not equate to the same degree of change at the bottom of the scale (e.g. a change in score from 10-18 is not equal to the same change from 2 to 10). Another weakness is that the BI is not sensitive to change at extremes of ability. These "floor" and "ceiling" effects mean that it is less discriminating in patients with severe or mild disabilities. The Barthel also omits other aspects, such as social, domestic or role functions related to quality of life and focuses solely on functional ability. However despite its limitations, the BI is one of the briefest assessments of ADL and is recommended by the UK Royal College of Physicians for routine use in assessment (Royal College of Physicians 2008).

6.6.3.1 Rationale for using the BI

The biggest strength of the BI is that it is fast and easy to administer, and takes only a few minutes at most to complete. Originally designed as an interviewer administered scale, the postal version has also shown good reliability (Gompertz, Pound and Ebrahim

1994) (Yeo, Faleiro and Lincoln 1995). The BI is also one of the most prevalent functional outcome scales used in stroke and rehabilitation research (Quinn, Langhorne and Stott 2011), and has been translated into several languages. It facilitates comparison with much of the existing research. Also no licensing fee was required for its use.

6.6.3.2 Reliability and validity of the BI

Internal consistency of the BI is generally described as good to excellent (α = 0.80-0.93) (Quinn, Langhorne and Stott 2011) and the level of inter-observer reliability is considered one of the strengths of the scale (Yeo, Faleiro and Lincoln 1995). In terms of validity, the BI was originally formulated for individuals with neurological and musculoskeletal disease, hence it is intuitive that it would be a valid measure for stroke. Close correlation between the BI and clinical data such as the extent of motor loss or nursing time, indicate good concurrent validity (Quinn, Langhorne and Stott 2011). Its construct validity is suggested by close association with other measures of activity, and the BI is so widespread that it is often used as the gold standard comparator in studies of novel ADL scales. The BI is also sensitive to change over time, with a two point difference (BI score 0-20) deemed to be clinically significant (Quinn, Langhorne and Stott 2011).

6.7 Exploring acceptability of research

Prior to carrying out the main study, questionnaire acceptability was evaluated using a convenience sample of interested stroke survivors who were known to the researcher and attending a local stroke club. Six individuals volunteered to review the contents of the questionnaire package that participants would receive. The primary purpose of involving these stroke survivors was to determine whether there were any concerns in filling out the illness perception questionnaire as it had not been used extensively in the stroke population. Upon completion, respondents were asked the following questions about acceptability:

1. What was their overall impression of the survey?
2. Were the questions what they expected given the topic?
3. Were they able to complete the survey on their own, and if not if they were able to obtain help?
4. Were the questions easy to read and understand?

5. Were any questions confusing?
6. Which questions were most difficult to understand and why?
7. Were there any questions they thought should be on the survey that were not?

Overall the response was positive. Individuals reported that they could understand all questions. One individual indicated that the Illness Perception section of the questionnaire was a bit long but they were still able to complete it.

6.8 Research approvals and considerations

Ethical approval for the project was granted by the Leeds East NHS Research Ethics Committee on February 21, 2011 for access to patients attending the Barnsley outpatient stroke clinic (Appendix G). Amendments for access to clinics in Sheffield was submitted on April 7, 2011 and approval received on April 21, 2011. A subsequent amendment of notification regarding change in the lead supervisor was submitted on July 5, 2011, and agreement received on July 14, 2011.

The process of obtaining informed consent needed to adhere to the principles of the Mental Capacity Act (2005). All stroke patients eligible for study participation were presumed to have mental capacity. Care was taken to minimise the burden of data collection for participants as the questionnaire pack was estimated to take 25-30 minutes to complete.

Data protection was another key issue that had to be considered. During the initial screening in the outpatient clinics personal details including name, address, and telephone number were collected from individuals who agreed to participate in the study. This information was assigned a unique reference ID number and all subsequent information collected from the participants (i.e. the questionnaire pack), was also assigned the same reference ID. Personal details and questionnaire responses were kept separately, and only linked during the analysis phase. Additionally, participants were instructed not to record their name or address details on the freepost envelope when returning the questionnaire pack.

The potential exists that in asking someone about their mood this may elicit unexpected negative emotional responses. In this study the Hospital Anxiety and

Depression Scale (HADS), was administered. Participants were made aware of their rights to refuse to answer any of the questions in the patient package if they so wished. The HADS assesses mood and so there was a possibility of discovering patients scoring within the clinical range for a possible mood disorder. However, given the research mandate of the protocol, confidentiality was not breached by relaying the findings back to the patient's stroke consultant or clinical care team. Stroke participants were routinely screened for mood during clinic appointments; as such they were not contacted if they had a high score on the HADS. If however, during the course of the screening process or during any other correspondence with the participant, it became apparent that they were seriously contemplating or planning to do harm to themselves or others (e.g. disclosure of planned suicide) this information would have been shared immediately with the clinical team responsible for patient care and the patient would have been made aware that such a notification had been made.

6.9 Research and Development

In addition to obtaining ethical approval for this study, all research conducted on NHS premises involving human participants, their tissue, or data must also receive research and development (R&D) governance approval (Department of Health 2005). An NHS wide coordinated approach to obtaining R&D approval has been established, however at the time of study initiation only studies that were adopted by the National Institute of Health Research (NIHR) portfolio system could obtain R&D approval using this coordinated approach across sites. This study was not a portfolio study and as a result individual R&D approvals needed to be obtained from each participating trust site.

The Barnsley Hospital Foundation Trust research governance committee granted access to Barnsley stroke sites on March 4, 2011. This was within two weeks of them receiving full documentation and a letter of access was granted allowing access to Barnsley clinics. Patient recruitment commenced at this site on March 21, 2011.

The process was less straightforward in Sheffield. Although approval for an honorary contract was approved on July 1, 2011, staffing turnover, and a multitude of administrative miscommunications resulted in not receiving R&D approval to access the site until September 1, 2011. The Sheffield clinic ran on the same day as the Barnsley clinic.

Recruitment in Barnsley ended on September 15, 2011. The commencement of other studies meant that recruitment at the Sheffield site was ended on November 24, 2011. In all, patient recruitment occurred between March 21- and November 24, 2011. This was two months longer than the original six months timeline estimated in the PhD work-plan (Table 6-2).

Table 6-2 Timeline of events for research ethics, R&D approval, and recruitment

	Feb 2011	Mar 2011	Apr 2011	May 2011	Jun 2011	Jul 2011	Aug 2011	Sep 2011	Oct 2011	Nov 2011
Ethics approval received										
Barnsley R&D approval										
Barnsley recruitment										
1st REC amendment to include Sheffield										
1st REC amendment approved										
Sheffield R&D approval										
Sheffield recruitment										
2nd REC amendment (New supervisor)										
2nd REC amendment approved										

6.10 Research Participants

All stroke patients presenting at the Barnsley or Sheffield Royal Hallamshire outpatient stroke clinics were eligible to participate in the study provided they met the following criteria :

6.10.1 Inclusion criteria

- Received a clinical diagnosis of first-ever ischaemic stroke or TIA.
- Were at least 18 years of age.
- Were less than five months post-stroke at the time of recruitment.
- Attended a stroke clinic in Barnsley or Sheffield, Yorkshire.

6.10.2 Exclusion criteria

- Had poor prognosis for survival to three months after the initial contact as determined by clinical opinion.
- Had more than one stroke at the time of initial contact (as it was thought that illness perceptions may differ from those that had survived multiple strokes).
- Non English speaking background or first language other than English.
- Had global aphasia at the time of initial contact.
- Had other significant terminal illnesses or conditions of neurological impairment such as dementia, Parkinson's disease, Huntington's disease, or significant co-morbidities as judged by clinicians, as to make participation in research inappropriate.
- Were unable to provide informed consent, as determined under the Mental Capacity Act.

Previous history of anxiety or depression was not considered a reason for ineligibility.

6.11 Sample Size

It was originally intended that recruitment would be carried out over six months from the Barnsley site. Preliminary findings from the literature indicated that prevalence of anxiety would be approximately 15% (Burvill *et al.* 1995; Sturm *et al.* 2004). In order to obtain a generalisable sample size, the following formula was used:

$$n=Z^2pq/e^2$$

Where

Z= the confidence level at 95%
P= the proportion of the sample with anxiety
Q= 1-P
e= level of error (estimated at 7-8%)

The required sample size corrected for sampling from a finite study population of approximately 300 stroke survivors was 61-75. Based on previous research the postal response rate was estimated at 80%, and fully completed questionnaire rate at 70% (Murray, Forster and Young 2007). Consequently an additional 27-33 stroke survivors needed to be recruited to ensure an adequate sample size. As this was an exploratory study a power calculation was not conducted, however the sample was of sufficient size to conduct

planned regression analysis whereby there would be a ratio of at least 5 cases per predictor variable (Peduzzi *et al.* 1996).

6.12 Participant recruitment and follow-up

Individuals were recruited in-person on their visits to the outpatient stroke clinics. At the start of every clinic patient files were reviewed by the chief investigator (ACB) to determine which patients were potentially eligible for study inclusion. A list of names was prepared and provided to either the consultant or stroke nurse specialist seeing patients on that day as a reminder for them to inform the patients about the study. In line with the research protocol and the principles of the Mental Capacity Act 2005 (Department of Health 2008), the attending clinician did not make any decisions about a patients capacity to participate, however if the individual had significant co-morbidities or were in a state as to make participation impractical (e.g. patients with dementia) they were not referred to the researcher for potential recruitment into the study. At the end of the clinic appointment patients meeting the study eligibility criteria were referred to the chief investigator at which point they were provided with a brief explanation of the study and a participant information sheet (Appendix E). At this point the referred patients had the opportunity to ask questions or seek clarification about the study. Written informed consent from those agreeing to participate was obtained at this time (Appendix F). Individuals who required additional time to think about participating, were provided with a consent form and freepost envelope to return should they decide they wanted to be part of the study at a later time. Those agreeing to participate were given a questionnaire pack to complete at home, along with a first-class freepost envelope for its return. All participants who agreed to participate in the study were sent the same package three months after recruitment into the study.

If completed questionnaire packs were not returned within two weeks of having been provided, participants were contacted by telephone. If they could not be reached by telephone they were sent a reminder letter. Those who had been reached by phone, but did not return the questionnaire within one week after the first follow-up call were subsequently sent a reminder letter as well. This method of contacting patients has been found to be the most effective at maximising participation in research using postal questionnaires (Nakash *et al.* 2006).

6.13 Data collection

Demographic information that consisted of recording participants' age, sex, living status (alone or not), and ethnicity, was collected (Appendix H). The pathological and clinical classification of stroke type were also recorded if they were available in the outpatient clinic file, and participants were asked if they had any history of anxiety or depression, and if yes, what sort of treatment they had received. Documentation of significant medical co-morbidities was obtained using the Katz co-morbidity questionnaire (Katz *et al.* 1996).

Additionally, during the recruitment process the brief Six Item Cognitive Impairment Test (6CIT) was administered to describe the study sample, but was not used to make decisions about participant eligibility. The Six Item Cognitive Impairment Test (6CIT) (Katzman *et al.* 1983) is a short test that screens for cognitive impairment and possible dementia. It consists of one memory, two calculation and three orientation questions. The test asks the participant what month and year it currently is, the approximate time of day, to count backwards from 20 to 1, to list the months of the year in reverse order, and to repeat and recall a short memory phrase. The 6CIT correlates very highly with the Mini-Mental State Exam (MMSE) (Folstein, Folstein and McHugh 1975) (Brooke and Bullock 1999) which is regarded as the gold standard in screening for cognitive impairment in the general patient population and which is widely used in clinical practice. Several studies have found the validity of the MMSE less than optimal for stroke survivors (Nys *et al.* 2005; Blake *et al.* 2002), and have suggested that the Montreal Cognitive Assessment (Nasreddine *et al.* 2005) or the Addenbroke's Cognitive Examination-Revised (Mioshi *et al.* 2006) tests are more appropriate measures by which to screen for cognitive impairment because they are more sensitive. However, the average time for administration of theses tests range from 10-20 minutes making their use impractical in a busy outpatient clinic. While the 6-CIT hasn't been validated in stroke, it has also been found to be more sensitive than in a sample of older patients (Brooke and Bullock 1999). The average administration time needed for the 6-CIT is also much shorter at only five minutes

Responses to the 6CIT are scored based on a weighted sum of the number of errors, with a score of 8 and above indicative of probable cognitive impairment. Recent validation

studies indicate that a score of 11 or more may be a more appropriate cut-off score for identifying possible cases of cognitive impairment to take into account differential educational levels evident in a clinical sample of older patients (Tuijl *et al.* 2011). Despite its ease and brevity in administration, the 6CIT is only recently starting to garner interest as a screening tool or means of describing cognitive impairment in stroke research. It was recently used in the Longer Term Unmet Needs After Stroke Trial, one of the largest ever clinical trials in stroke rehabilitation (Stroke Research Programme 2012). Additionally, the 6CIT is now recognised by the Royal College of General Practitioners as a method of screening for cognitive impairment and its usage continues to increase (Royal College of General Physicians 2010). It is important to highlight that in this study the 6CIT was not used as a primary measure, rather it was administered to patients who agreed to participate as a proxy measure for describing the cognitive status at the time of recruitment (Appendix H).

6.14 Data storage and handling

Study participants were given a researcher assigned reference identification number upon agreeing to take part in this study. Questionnaires were marked with this code and participants identified by it. Participant data were stored on a secure password protected university computer drive that was only accessible to the chief investigator. All returned questionnaires were stored in a locked filling cabinet in the School of Healthcare at the University of Leeds in accordance with the storage guidelines specified by the Research Council UK Code of Conduct on the Governance of Good Research Conduct.

6.15 Statistical Analyses

The following section provides a general overview of statistical methods and techniques used throughout the study.

6.15.1 Data exploration and missing data

Error checking of data occurred by running frequency distributions for all variables to verify that values were valid. Where suspect or incorrect values were found, the original questionnaire was referenced and necessary changes made. The level of missing data across individual variables was also assessed as this can influence the validity and reliability

of results. As a general rule any variable containing missing data on 5% or fewer of cases can be ignored.(Tabachnick and Fidell 2007) All missing variables were cross-checked with the original questionnaire to verify that they were not caused by data entry error.

Both the Shapiro-Wilkes test (Shapiro and Wilk 1965) and quintile-quintile (q-q) plots were used to examine the univariate normality of continuous variables. Outliers in data were examined with a z-score. A z-score (Data point - Mean score of the data point)/ Standard deviation) greater than 3.29 was considered significant (Tabachnick and Fidell 2007), and analysis was re-done excluding the outlier(s).

6.15.2 Baseline cross-sectional analyses

Univariate descriptive analyses (e.g. means, median, frequency distribution) were conducted for key demographic and clinical variables of interest. Differences between groups (i.e. responders vs. non-responders OR anxious vs. non-anxious) at baseline were assessed using studentized t-tests, Chi-square, or Mann-Whitney U test depending on the distribution. A p-value <.05 was used for evaluating significance.

6.15.2.1 Internal Reliability of the IPQ-R

As the IPQ-R had not been used extensively within the stroke population, tests for internal reliability were conducted and compared with findings in other stroke populations. The IPQ-R evaluates individual illness perceptions by asking multiple questions about each of the eight domains. This is advantageous for several reasons. First, individual questions may be unreliable and are subject to considerable random measurement error. However the effect of this error averages out when individual scores are summed to obtain a total score. Second an individual item can generally only categorise people into a small number of groups and cannot discriminate among fine degrees of an attribute; as such it can lack precision. Lastly individual questions lack scope, making it difficult for them to fully represent a complex theoretical concept or specific attributes. The internal consistency of the IPQ-R domain scores were evaluated by calculating Cronbach alpha statistics. Cronbach's alpha (α) assesses whether the items included within a domain tap only the intended dimension. Cronbach alpha scores range between 0 and 1, with a score of ≥0.70-0.80 considered acceptable, >0.80-0.90 good, and >0.90-1.00 excellent (Bland and Altman

1997). The IPQ-R values from a stroke study, and the original test population for the IPQ-R were included for comparison purposes. The internal reliability coefficients for the HADS and the Barthel Index were also examined even though they have been used extensively in stroke.

6.15.2.2 Correlations

Bivariate Spearman rho correlations (range 0 to 1) were calculated to assess inter-relationships between the illness representation domains. As several of the variables in the correlation matrix were to be entered into the regression model, coefficients with values larger than 0.9 were deemed significant (Tabachnick and Fidell 2007), and a decision would have been taken as to which variable should be entered into the regression model.

6.15.2.3 Multivariate Analysis of Variance (MANOVA) and Discriminant analysis

Given the published research has largely separated post-stroke anxiety and depression, a multivariate analysis of variance (MANOVA) (Tabachnick and Fidell 2007) was conducted to assess differences in illness perceptions between participants with anxiety, depression, or neither. A hierarchical approach was used to categorise individuals into either the anxious or depressed group. Hence, if an individual had co-morbid anxiety and depression they were classified as depressed. All eight of the individual illness representations were entered into the MANOVA as dependent variables. MANOVA allows for simultaneous comparison between the groups and reduces the chance of Type one error (i.e. concluding groups are significantly different when they are not). Essentially, MANOVA produces one composite variable score which determines whether there is a difference between the individual group means, after taking into account the correlations that exist between the test variables. The significance of the composite score was assessed using the Pillai's trace F-test.

MANOVA assumptions were assessed using the following tests:

1. Assumption of Normal Distribution of dependent variables: The Shapiro-WIlks test in the data exploration phase indicated that the individual IPQ-R domain scores were normally distributed

2. Assumption that the error variance of the dependent variables is equal across the three groups: The Levene's F tests were used. If the test was significant at $p<.05$ then the conclusion would be that the variances were significantly different
3. Assumption of equality of covariance which examines the extent to which the covariance of the dependent variables are similar for each of the groups: The Box-M test was used. As this test is highly sensitive, it is suggested that a value of $p<.01$ be used to determine significance (Tabachnick and Fidell 2007).

A separate post-hoc analysis with a Bonferroni correction significance set at $p<.01$ was carried out to identify which individual IPQ-R domain scores the groups differed. Additionally, it is advised that a significant MANOVA analysis be followed up with a discriminate analysis (Tabachnick and Fidell 2007). The methods associated with discriminant analyses are more complex, and as such they have been described in detail in their respective results section in chapter seven.

One of the primary aims was to identify illness perceptions and clinical factors that were associated with, and predictive of, anxiety at baseline and over time. A multi-stage approach was necessary. This section provides a brief overview of the techniques used. Specific details of the models and tests used are described in the relevant sections in the results chapter.

6.15.2.4 Regression analysis

An analysis of covariance (ANCOVA) was carried out to identify predictors of baseline anxiety levels. In the first step, age, sex (0=male, 1= female), history of anxiety or depression (0=no, 1=yes), and the Barthel Index score were entered into the model. The individual IPQ-R domain scores were entered into the second step. The adjusted R-square value was used to assess the proportion of variance explained by the model at each step. The variance inflation factor (VIF) was used to evaluate the level of statistical multicollinearity. A VIF <5 was considered acceptable (Tabachnick and Fidell 2007). The distribution of regression residuals along with the Shapiro-Wilks test were used to determine whether the regression residuals were normally distributed. An absolute value of three was used to identify outliers in the residuals (Tabachnick and Fidell 2007). Normal

probability plots were used to evaluate linearity of the residuals, and scatterplots to assess homoscedasticity (constant variance) of the observations in the dataset. Finally, data points that could be inserting undue influence on the regression coefficients were examined by investigating the Leverage values. Leverage values above the critical cut-point of 3p/n where (p=number of predictors, and n= number of observations) were considered significant. For this data set the critical Leverage value was 0.513. If any observations had a Leverage value above the critical value, they would be removed and the regression analysis subsequently rerun to see whether there would be changes in regression results.

6.15.3 Longitudinal analyses

Univariate analyses were carried out to test for differences between individuals lost to follow-up and those who returned time two questionnaires. Chi-square, t-tests, and Mann-Whitney U tests were used to assess significance. Simple change scores for anxiety, depression, and the Barthel Index were calculated by subtracting scores at time 1 from scores at time 2. As the data collected were from repeated measures in the same group, paired statistical tests were used. These included McNemar's and Wilcoxon signed rank sum tests, and paired t-tests.

A repeated measures MANOVA was conducted to compare IPQ-R domain scores at baseline with scores at follow-up. Illness representation data were collected on more than one occasion, hence there was an opportunity to conduct cluster analysis which could classify individuals into subgroups according to their change in illness representations from baseline to three-month follow-up.

6.15.3.1 Cluster analysis

Cluster analysis is a descriptive statistical technique that is used to identify groups of similar individuals. It has value as a means of analysing illness representations that take into account an individual's entire illness schema (Clatworthy *et al.* 2007). Evaluating an illness profile may be more meaningful and easily interpreted than assessing individual IPQ-R domains. Additionally, cluster analysis is useful when carrying out regression analyses in a small sample as it reduces the number of variables that need to be entered into the model. Cluster analysis was carried out to assess changes in overall illness schema over time, and to

assess whether these illness beliefs were associated with anxiety at follow-up. The methods associated with the cluster analysis are described in detail in chapter eight.

6.15.3.2 Structural Equation Modelling & Regression Analysis

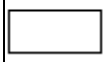
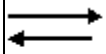
For the longitudinal analysis an ANCOVA adjusting for baseline anxiety using the same approach described in section 6.15.2.4 and structural equation modelling, were conducted to identify predictors of anxiety at follow-up. ANCOVA analysis is useful for understanding the role that individual covariates have on an outcome variable. Additionally, this was an exploratory study and it was thought there may be other important associations that existed between the predictor variables that were of interest but would not be apparent if only the ANCOVA was conducted. Subsequently, both an ANCOVA and Structural Equation Modelling (SEM) were carried out with the aim of the former to identify predictors of anxiety at follow-up. The latter SEM also has the ability to predict anxiety at follow-up, however it can also uncover other potentially important associations between the regression model covariates in their pathway to predicting anxiety that would only be possible by conducting multiple ANCOVA analyses. SEM and its assumptions are described below.

SEM is a relatively new and powerful multivariate technique. The primary goals of SEM are to understand the patterns of correlation and covariance between a set of variables, and to explain as much of their variance as possible with the model that is specified (Blunch 2008). Factor analysis, path analysis, and regression all represent special cases of SEM. The advantages of SEM are that it is flexible and allows for relationships between multiple independent and dependent variables to be examined within one model. Observed and unobserved variables can be included, and it recognises that variables are measured with error and takes this into account when calculating parameter estimates. In traditional regression, variables entered into a model are assumed to have been measured without error. This section provides a general overview of the SEM approach that was used in chapter eight.

To start, the language used in SEM is different from that of traditional regression. Within SEM independent variables are known as *exogenous variable*s, while dependent variables are called *endogenous variable*s. The exogenous and endogenous variables can be

measured directly or as latent constructs. A Latent construct variable is a hypothetical variable¬ that is not directly measured but rather assumed to be directly related to the observed variables (e.g. personality). Disturbance, another term used within SEM is defined as the unspecified cause(s) of an endogenous variable and is akin to an error or residual in a prediction equation. Finally, the graphical language associated with SEMs allows for a pictorial display of complex relationships between variables which is transformed into a set of equations. The set of equations are solved simultaneously to test model fit and estimate parameters. Table 6-3 shows the common symbols used in SEM diagrams.

Table 6-3 Common symbols used in SEM

Symbol	Description
	Observed variable- a variable that has been directly observed
	Latent Variable(factor or construct)
	Unidirectional effect(e.g. X is a predictor of Y)
	Reciprocal effect (e.g. X is a predictor of Y, and Y is a predictor of X)
	Correlation or covariance

Compared to traditional regression techniques, SEM is more flexible in its assumptions and allows both confirmatory and exploratory modelling. Hence it is suited to both theory testing and theory development. It is able to model mediating variables, and the flexibility of SEM allows for simultaneous comparison of models making different assumptions regarding causal association.

Disentangling the differential association between multiple illness representations with anxiety was the primary goal of the empirical study. To start, anxiety is highly correlated with depression. SEM was considered because, unlike regression, multiple correlations between independent variables could be evaluated within one model. Additionally, other indirect relationships that may occur within the model but which cannot be assessed using a regression model could also be evaluated. Figure 6-2 provides a graphical example of a SEM. In this figure independent variables (IV) 1-3 predict dependent variable anxiety and

depression. Furthermore the indirect effect of the three independent variables on anxiety as mediated by depression, could also be specified.

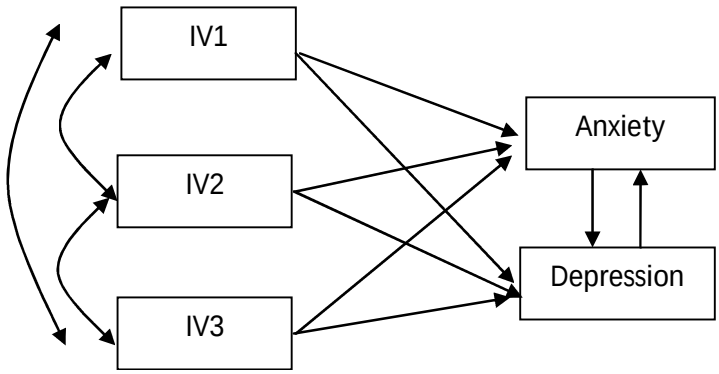


Figure 6-2 Example of modelled relationships using SEM

Similar to regression analysis, model parameters are determined by model estimation. Maximum likelihood (ML) estimation is the default for estimating model parameters. The estimates are assumed to be population values, hence ML seeks to maximise the probability that the data were drawn from the population. Maximum likelihood estimation is also appropriate for non-normally distributed data and small sample sizes. The fundamental question in SEM is how well the model derived from the data fits with the actual sample data. It does this by assessing whether the observed covariance matrix from the sample data fits or is similar to the estimated (proposed model) covariance matrix, and this is done by using the Chi-square test which assesses the deviation between the estimated covariance matrix and the observed covariance matrix. Chi-square is considered a "badness of fit" test. This is because a non-significant Chi-square is desired because it suggests that the reproduced and observed covariance matrices do not differ significantly and that the data fit the proposed model structure. The Chi-square statistic is sensitive to sample size and will often be significant in large samples (Iacobucci 2010). As a result, other fit indices are used in conjunction with the Chi-square test to inform the relative fit of a model. Table 6-4 provides a summary of commonly reported fit indices.

The first of these fit indices is the Comparative fit index (CFI). The CFI is based on the ratio of the Chi-square of the tested model and the independence (null) model. The independence model assumes there is no correlation among any of the variables in the

model. It represents the extent to which the model of interest is better than the independence model. Values that approach 1 indicate acceptable fit. CFI is not sensitive to sample size.

The Normative fit index (NFI) is another fit index with values that range between 0 and 1, where 1 is ideal. The NFI is equal to the difference between the Chi-square statistic of the independence model and the Chi-square of the model of interest, divided by the Chi-square statistic of the independence model. For example, and NFI of .90 indicates that the model of interest improves the fit by 90% relative to the independence model. The NFI is sensitive to sample size and may be underestimated where sample size is small, and can be overestimated if the number of model parameters is increased. The Tucker-Lewis index (TLI) is similar to the NFI except that it will penalise (i.e. yield a lower estimate) more complex models with more parameters, but is relatively independent of sample size. Generally values over .90 or .95 are considered acceptable.

Other fit indices include the Root mean square error of approximation (RMSEA). The RMSEA evaluates the extent to which the model of interest fails to fit the data per degree of freedom. It generally will favour more complex models. RMSEA values <.05 are considered good, <.08 acceptable, and >.1 not acceptable. Finally the Akaike information criterion (AIC) is considered when testing alternative models with the same data that are not nested or hierarchically related. The absolute value of the AIC is irrelevant, however models with the lowest value are optimal. It reflects the extent to which the observed and predicted covariance matrices differ from each other, however unlike the RMSEA it penalises more complex models.

Table 6-4 Summary of common SEM fit indices

	General rule for acceptable fit
Absolute fit index	
Chi-square (X^2)	Ratio of X^2 to df ≤ 2 or 3 good
Comparative fit indices	
Comparative fit index (CFI)	Range between 0 and 1. Represent the extent to which the model of interest is better than the independence model. Not sensitive to sample size. ≥0.95 is acceptable
Normed fit index (NFI)	Range between 0 and 1. Estimates how much proposed model improves the fit relative to the independence model: ≥0.95 is acceptable. Underestimated when sample size is small
Tucker- Lewis Index (TLI)	Similar to NFI, values over .90 considered acceptable
Other indices	
Root Mean Square Error Approximation (RMSEA)	Evaluates the extent to which a model fails to fit the data Values <.05 good, <.08 acceptable, >0.1 not acceptable
Akaike information criterion (AIC)	Penalises more complex model, but not sensitive to sample size. Good for model comparison

6.15.4 Statistical Software

All analyses were performed using PASW Statistics v.18 (SPSS, Inc, 2009 Chicago, IL). AMOS (Arbuckle 2006) was used to conduct the structural equation modelling.

6.16 Summary

The general design and methods used for the empirical study have been described, including the measurement of anxiety, illness representations, and functional and cognitive impairment. Analysis techniques have been described, and an overview of structural equation modelling provided.

7 Chapter Seven: Study 3- Results Baseline analysis

7.1 Introduction

The empirical study results have been divided into two parts. Part one provides descriptive information about individuals recruited into the study, and demographic and clinical variables of interest. The reliability of the instruments used were evaluated, and scores on the IPQ-R domains compared with a stroke study, and the original IPQ-R test sample. The prevalence of anxiety along with impairment in activities of daily living and cognitive impairment at time of recruitment were assessed. Statistical significance tests of key variables, stratified by anxiety status have also been presented. Finally, a multivariate analysis of variance (MANOVA) along with a discriminant analysis to test for differences between anxious and non-anxious participants explained, and a multivariate linear regression model predicting anxiety at baseline is provided.

7.2 Participation

Recruitment into the study occurred over a period of eight months between March 2011 and November 2011. During this eight month recruitment period, a total of 298 individuals were scheduled for clinic appointments. Approximately one-third of patients were attending for reasons other than stroke (n=97), and over 10% (n=38) had previously had a stroke or had severe co-morbidities such as dementia or Parkinson's disease (n=8). A total of 155 stroke patients were potentially eligible for participation in this study, of which 104 (67%) patients were recruited and 80 (77%) returned the baseline questionnaire. Overall 52% (80/155) of the eligible population participated in the study (Figure 7-1).

Patient non-attendance at clinic appointments was the leading reason for exclusion (n=16). Other reasons for exclusion included refusal to participate (n=13), or presence of severe communication difficulties (n=3). There were occasions when clinicians did not refer patients to the researcher (n=9); however this only occurred during the early stages of the study when there was some turnover in staff running the clinic. Additionally on four occasions reminder tags that were attached to the patient files as referral reminders fell off, resulting in these patients being missed.

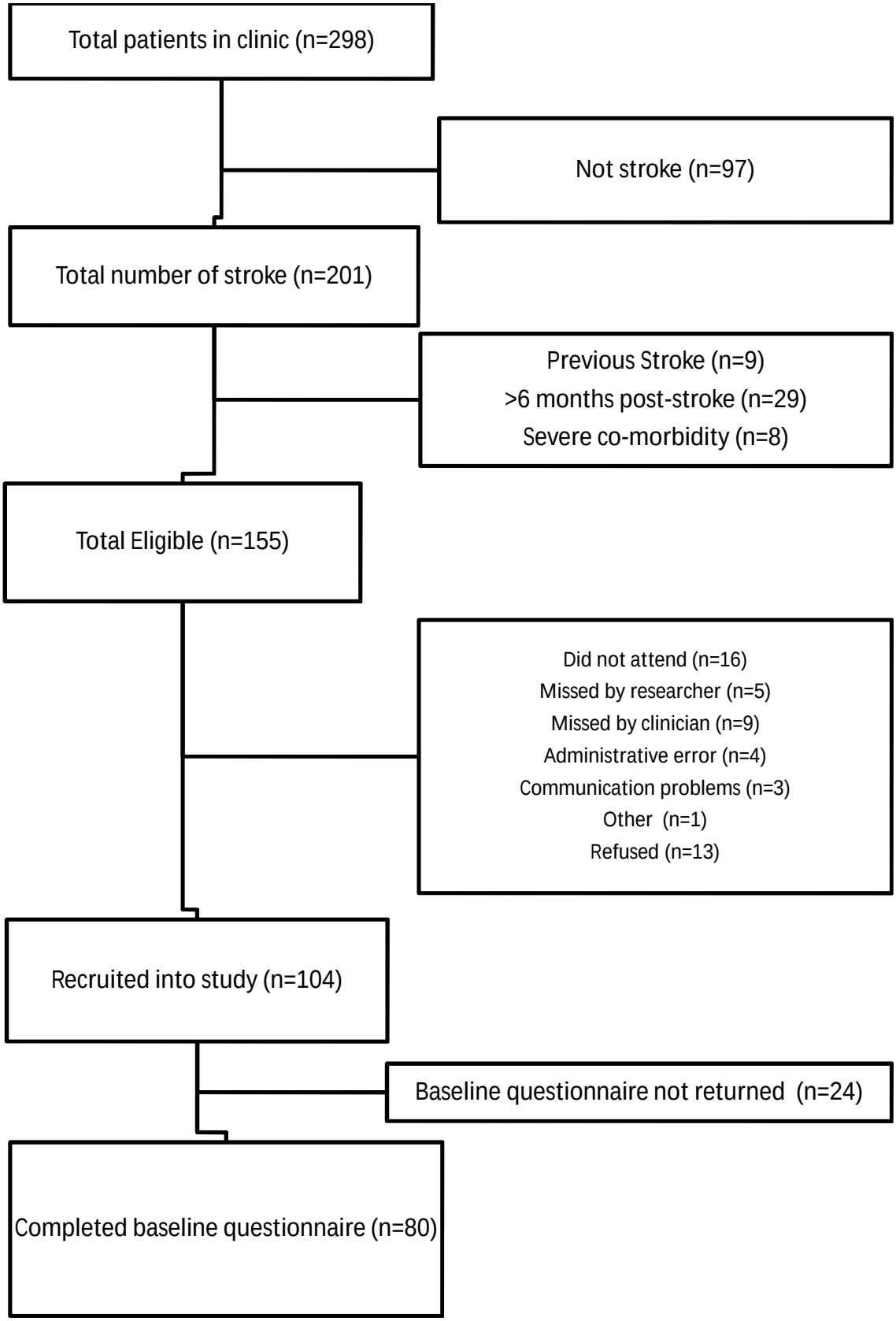


Figure 7-1 Participant recruitment flow diagram

7.3 Responders compared with non-responders at baseline

To evaluate whether there were differences between those patients that responded compared with those that did not, a series of univariate descriptive analyses using chi-square and Mann-Whitney tests were conducted (Table 7-1).

7.3.1 Demographic and clinical variables

The mean age of the total recruited sample was 69 years (SD=12.7), of which 55 (53%) were male. Non-responders did not differ significantly on any demographic factors, however they were on average younger than responders (64 years vs. 70 years), and differential response rates were observed for those under 65 years of age as compared to those who were 65 years or older (37% vs. 84%, X^2= 4.75, p=0.03). In terms of clinical variables non-responders had significantly higher mean scores on the 6-CIT cognitive impairment test (range 0-28) administered at recruitment than those that responded (9.7 vs. 6.0, p=.004). Two individuals (one with a stroke and the other with a TIA) had extremely high scores of 28 on the 6-CIT. The difference between responders and non-responders remained significant even after excluding these two individuals from the analysis (U=546, p=0.01). Non-responders had had more time past since their stroke (12 weeks vs. 9 weeks), and were more likely to have a history of anxiety or depression (37% vs. 19%) relative to those that responded. The response rates were similar for the two recruitment sites (76% Barnsley vs. 80% Sheffield). Classification according to the Oxfordshire Community Stroke Classification system was only available for 43 patients, with half (n=22) recorded as having a left hemisphere stroke. Analysis by ethnicity was not conducted as all but two individuals recruited into the study self-identified as White British.

Table 7-1 Characteristics of responders vs. non-responders

	Total (n=104)	Non-responders (n=24)	Responders (n=80)	Significance
Demographic				
Age in years				
Mean (SD)	68.9 (12.7)	64 (15.6)	70.3 (11.4)	U=752, p=.11
Median	72	62.5	73	
<65 years: n(%)	35 (34)	13 (54)	22 (28)	
Sex: n(%)				
Female	49 (47)	10 (42)	39 (49)	X^2= .37, p=.54
Male	55 (53)	14 (58)	41 (51)	
Live Alone: n(%)				
No	67 (64)	15 (63)	52 (65)	X^2= .39, p=.82
Yes	36 (36)	9 (37)	27 (34)	
Recruitment location: n(%)				
Barnsley	79 (76)	19 (79)	60 (75)	X^2= .18, p=.68
Sheffield	25 (24)	5 (21)	20 (25)	
Clinical Factors				
Type of Stroke: n(%)				
Cerebral Infarction	58 (56)	12 (50)	46 (57)	U=848, p=.32
TIA	41 (39)	9 (38)	32 (40)	
Intracerebral hemorrhage	4 (4)	2 (8)	2 (3)	
SAH	1 (1)	1 (4)	0	
Hemisphere location: N=43				
Right	21	6	15	
Left	22	5	17	
6CIT				
Mean (SD)	6.8 (5.5)	9.7 (6.1)	6.0 (5.1)	U=569, p=.004
Median	6	8	5.5	
IQR	2-10	6-12	2-10	
History of anxiety or depression: n(%)				
No	80 (77)	15 (63)	65 (81)	X^2= .3.66, p=.06
Yes	24 (23)	9 (37)	15 (19)	
Smoking status: n(%)				
No	75 (72)	15 (63)	60 (75)	U=804, p=.38
Yes	11 (11)	6 (25)	5 (6)	
Ex-smoker	14 (14)	2 (8)	12 (15)	
Number of co-morbidities: n(%)				
0	42 (40)	10 (42)	32 (40)	U=941, p=.88
1	40 (39)	9 (38)	31 (39)	
2	16 (15)	4 (16)	12 (15)	
3	6 (6)	1 (4)	5 (6)	
Time post-stroke at recruitment (weeks)				
Mean (SD)	9.9 (7.4)	12 (7.3)	9.2 (7.3)	U=716, p=.06
Median	7.0	10.5	7.0	
IQR	4-16	5.5-18	3.5-13	

X^2- Chi-square, U- Mann Whitney test

7.4 Instrument reliability analysis-

This section presents findings of the Cronbach alpha coefficients that were calculated to examine the internal consistency of the IPQ-R, the HADS, and the Barthel Index that were used in this study (Table 7-2).

7.4.1 Illness Perception Questionnaire (IPQ-R)

Cronbach alpha coefficients were calculated for the individual IPQ-R domains and compared with data from an unpublished stroke study that assessed the association between illness representations and depression (Ford 2007) , and also with the original test sample for the IPQ-R that consisted of a diverse group of over 700 individuals with various long-term conditions (Moss-Morris *et al.* 2002).

All domains showed good reliability. Alpha was slightly lower for the personal control domain however the level observed in this study was still acceptable. On the timeline (acute/chronic) alpha improved from 0.80 to 0.87 after removing the following three questions: 1) My stroke symptoms will last a short time, 2) The effects of my stroke will pass quickly, and 3) My stroke symptoms will improve in time. Additionally the coherence domain alpha scores improved slightly from 0.84 to 0.86 when the questions "I have a clear picture or understanding of my stroke" was dropped. However as results from this study will be compared with the existing literature, the total composite sub- scale scores on these two domains were used in all subsequent analyses. Overall the alpha scores observed in this study were similar to those seen in the large sample on which the IPQ-R was originally tested.

7.4.2 Hospital Anxiety and Depression Scale (HADS)

Both the anxiety and depression subscales of the HADS demonstrated good internal reliability. The reliability coefficient for the anxiety subscale was 0.86 and was 0.83 for the depression subscale. The reliability coefficient for the overall scale was 0.90.

7.4.3 Barthel Index

The reliability coefficient was lower for the Barthel index at 0.68. However no improvement was observed by deleting any of the items in the scale.

Table 7-2 Cronbach alpha's for the IPQ-R, HADS, and Barthel Index

Scale (Number of questions)	Present Study n=80	Ford Stroke study (2007) n=40	Original IPQ-R test sample n=711
IPQ-R			
Identity (22)	0.87,	-	-
Timeline- acute/ chronic (6)	0.80/ *0.87 (3)†*	0.86	0.89
Timeline- cyclical (4)	0.84	0.52	0.79
Consequences (6)	0.84	0.81	0.84
Personal Control (6)	0.72	0.54	0.81
Treatment Control (5)	0.80	0.49	0.80
Coherence (5)	0.84/ *0.86 (4)†*	0.83	0.87
Emotions (6)	0.85	0.84	0.88
HADS			
Anxiety subscale (7)	0.86	-	-
Depression subscale (7)	0.83	-	-
Barthel Index (10)	0.68	-	-

†- Improved Cronbach alpha score after the removal of select questions. Number in brackets indicate number of questions contributing to modified scale score.

7.5 Study population

The following section describes the 80 participants who completed questionnaires at baseline. These individuals will be referred to throughout as the study sample.

All study participants were diagnosed with stroke confirmed by computer tomography scans (CT) or magnetic resonance imaging (MRI). The nature of the stroke varied across participants. Forty-eight had a cerebral infarction, while 32 individuals had a TIA. Another two individuals (2%) had an intra-cerebral haemorrhage.

Amongst those that responded, 28 (35%) individuals indicated they needed assistance to complete the questionnaire. Having someone read the questions to them was the most frequently cited means of help (n=24), followed by someone discussing questions with them (n=3), someone ticking the boxes on their behalf (n=1), and reasons not specified (n=1).

7.5.1 Activities of Daily Living and cognitive impairment

Impairment in activities of daily living as assessed by the Barthel Index (BI) (0 to 20 scale), with higher scores indicative of less impairment found that the mean BI score was 17.1 (SD= 3.3), range 6 to 20 (Figure 7-2). The distribution of the BI scores were negatively skewed, indicating the study sample had lower levels of impairment. Close to a third (n=26) of the study sample obtained the maximum score of 20.

The 6-CIT scores (0 to 28 scale) were positively skewed, indicating low levels of possible cognitive impairment at recruitment in the study sample, with 85% (n=69) having a score of less than 11 (Figure 7-3).

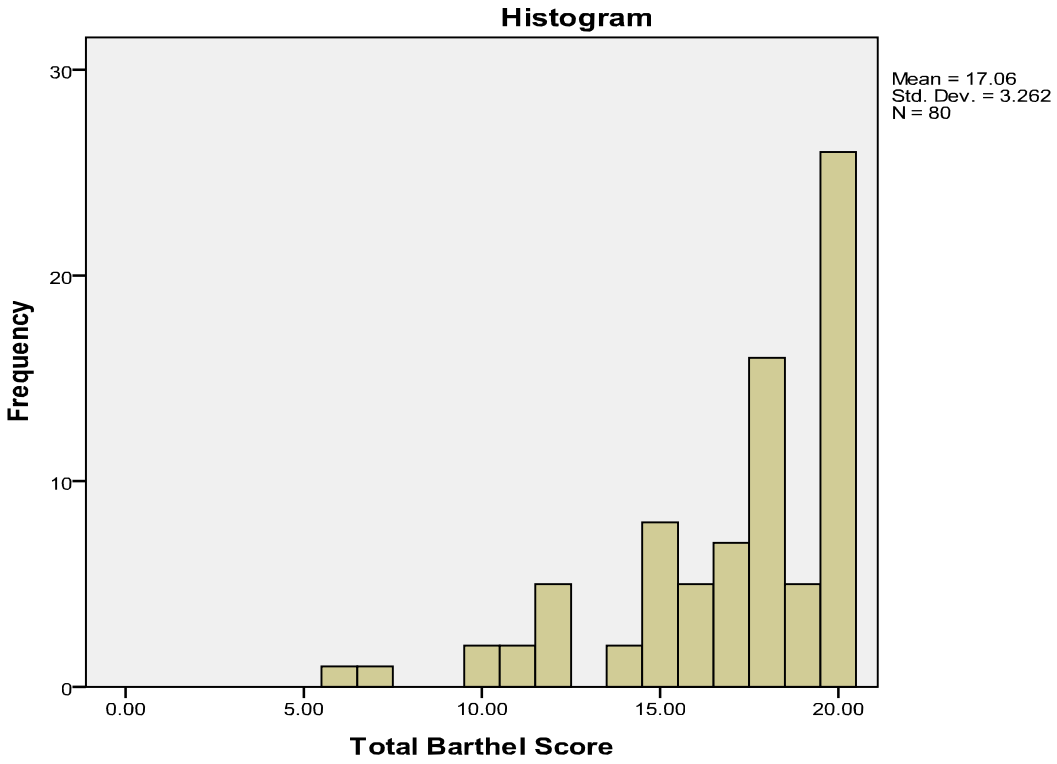


Figure 7-2 Distribution of Barthel Index scores at baseline

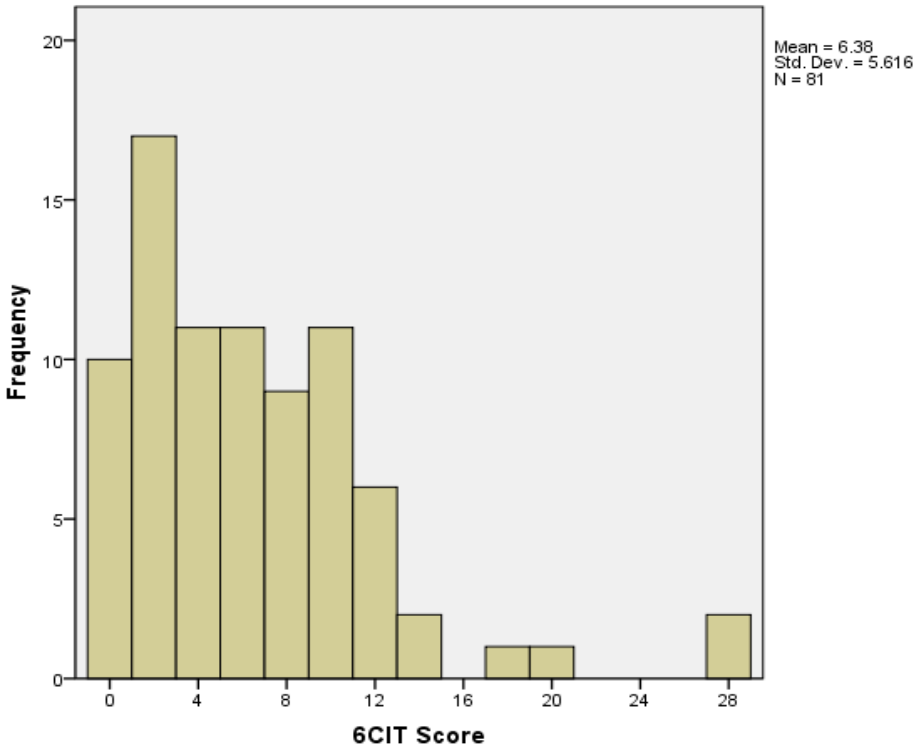


Figure 7-3 Distribution of 6-CIT scores at baseline

7.5.2 Anxiety prevalence and symptom severity

The prevalence of anxiety (HADS-A ≥11) at baseline is shown in Table 7-3 In total 30% (n=24) of the study sample was classified as having anxiety, (either alone or co-morbid with depression), and 5% (n=4) had depression alone (HADS-D≥11). Of those with anxiety 42% (n=10) had co-morbid depression.

Table 7-3 Prevalence of anxiety at baseline (n=80)

	Frequency (%)	Mean HADS-A Score (SD)	Mean HADS-D Score (SD)
No anxiety or depression	52 (65.0)	4.7 (3.1)	4.2 (3.1)
Anxiety only	14 (17.5)	11.9 (1.0)	7.4 (1.9)
Anxiety + Depression	10 (12.5)	14.0 (1.0)	13.4 (2.0)
Depression only	4 (5.0)	4.8 (3.7)	11.8 (0.5)
Total	80 (100)	7.1 (4.6)	6.3 (4.3)

The severity of anxiety (and depression) symptoms were also assessed by examining the mean and standard deviation scores for both HADS subscales (0 to 21 scale). Anxiety symptom subscale scores ranged from 0 to 16, and the mean anxiety symptom subscale score was 7.1 (SD= 4.6). Scores on the depression subscale also ranged from 0 to 16, with a mean score of 6.3 (SD=4.3) (Figure 7-4). A paired sample t-test showed that anxiety subscale scores were significantly higher than depression subscale scores at baseline (t=2.13, df=79, p=0.04)

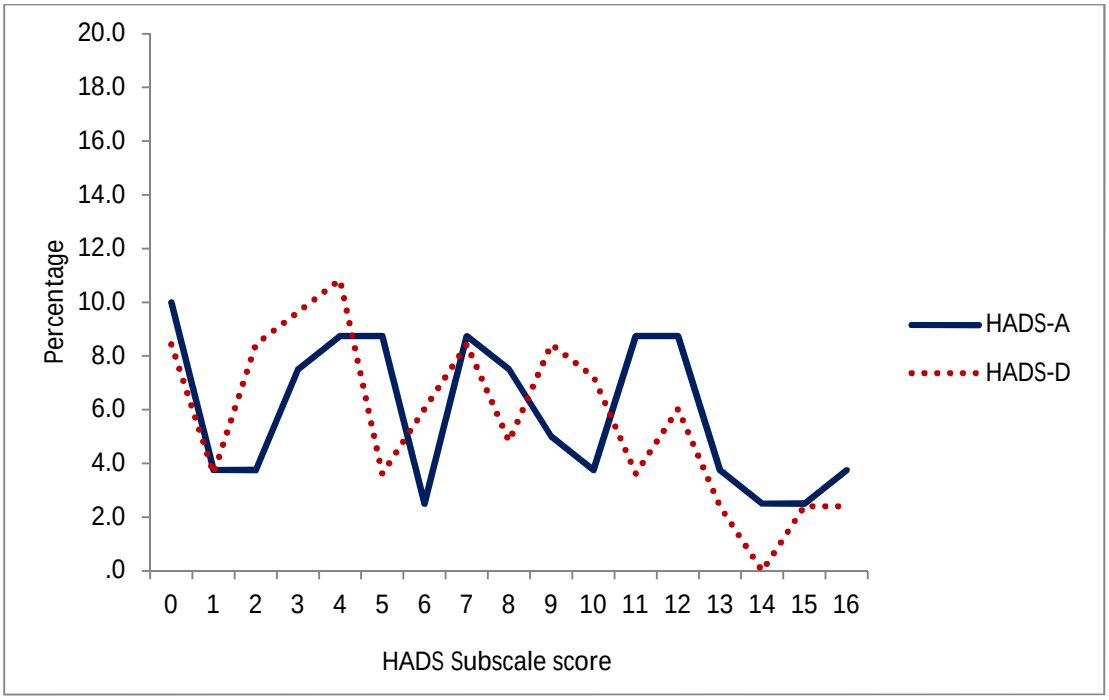


Figure 7-4 Distribution of HADS-A and HADS-D scores at baseline (n=80)

Table 7-4 shows univariate testing stratified by anxiety status at baseline (HADS-A ≥11 vs. HADS-A<11). Impairment in activities of daily living as measured by the Barthel Index, was significantly greater amongst anxious participants than the non-anxious, and a greater proportion of younger stroke survivors were anxious, however the difference was not significant at p<.05. Additionally, the proportion of individuals with a pre-stroke history of anxiety or depression was greater in the anxious group relative to the non-anxious group (29% vs 14%), however this difference did not reach statistical significance. Amongst those who indicated they had a pre-stroke history of anxiety or depression, 40% claimed they had not received any form of treatment for those episodes, and 60% indicated they had taken some form of drug therapy. None indicated they had received any psychological therapy.

Table 7-4 Characteristics of participants with and without anxiety

	No Anxiety (n=56)	Anxiety (n=24)	Significance
Age (in years)			
Mean (SD)	71.4 (11.3)	67.8 (11.4)	U=542, p=0.17
Median	73	69.5	
<65 yrs, n(%)	12 (21%)	10 (42%)	X^2= 3.45, p=0.06
Sex			X^2= 0.40, p=0.53
Female	26 (46%)	11 (46%)	
Male	30 (54%)	13 (54%)	
History of Anxiety or Depression			Fisher, p= 0.13
No	48 (86%)	17 (71%)	
Yes	8 (14%)	7 (29%)	
Lives Alone			X^2= 0.32, p=.57
No	36 (64%)	17 (71%)	
Yes	20 (36%)	7 (29%)	
6CIT			U=553, p= 0.30
Mean Score	5.83 (5.6)	6.25 (3.7)	
Median	4	6	
Range	0-28	0-13	
Number of Comorbidities			U=599, p=0.42
0	23 (41%)	9 (38%)	
1	23 (41%)	8 (33%)	
2	8 (14%)	4 (17%)	
3	2 (4%)	3 (12%)	
Smoking Status			U=565, p=0.53
No	42 (75%)	18 (75%)	
Yes	3 (18%)	2 (17%)	
Ex-Smoker	10 (5%)	2 (8%)	
Type of Stroke			X^2= 0.78, p=0.77
Stroke	33 (59%)	15 (63%)	
TIA	23 (41%)	9 (37%)	
Barthel Index Score			U=444, p=0.01
Mean (sd)	17.8 (2.4)	15.4 (4.2)	
Median	18	17	
Range	10-20	6-20	
Time Post-Stroke at recruitment (in weeks)			U=642, p=0.75
Mean (SD)	9 (7.1)	11 (8.2)	
Median	7	8	
Range	1-29	1-33	
Time Post Stroke Questionnaire Completed (in weeks)			U=612, p=0.53
Mean (SD)	9.7 (7.2)	11 (8.2)	
Median	7.5	8	
Range	2-32	1-34	

7.6 Illness representations at baseline

The following section describes illness representations observed in the study sample at baseline.

7.6.1 Frequency and attribution of illness symptoms

Participants were given a list of 24 illness identity symptoms and asked to indicate (i.e. Yes/ No) whether they had experienced any of them since having their stroke, and if so whether they believed they were related to their stroke.

Table 7-5 shows fatigue was the most commonly reported symptom experienced by participants at baseline, with 73% endorsing it. Forgetfulness, loss of strength, and stiff joints were also prevalent and reported in close to two-thirds of the study sample. Symptoms commonly associated with anxiety such as difficulty breathing, headache, sleeping problems, dizziness, and tingling in extremities were experienced by about half of all respondents. Less than 25% reported experiencing sore throat, wheeziness, or upset stomach. Close to one-third of participants said they had experienced symptoms of emotionalism (e.g. feeling upset or weepy), and 15% of the study sample reported paralysis. Participants reported experiencing multiple symptoms at baseline (mean= 9.0, median=9, range= 0 -21).

Participants did not always attribute the symptoms they were experiencing to their stroke. For example, more than a quarter of participants with fatigue did not believe that it was related to their stroke, and close to half of those with pain did not attribute the pain to their stroke. On the other hand, virtually all individuals who reported speaking problems, paralysis or feeling upset or weepy, attributed these symptoms to their stroke. Hence while participants experienced an average of nine symptoms post stroke, the mean number attributed to stroke was six (Table 7-6).

Table 7-5 Frequency of illness (identity) symptoms experience post stroke and believed to be associated with stroke at baseline

	Experienced symptom since stroke (%)	Experienced symptom and attributed it to stroke (%)
Pain	34/80 (43)	19/34 (56)
Sore throat	11/80 (14)	2/11 (18)
Nausea	22/80 (28)	13/22 (59)
Breathlessness	40/80 (50)	16/40 (40)
Weight loss	26/80 (33)	17/26 (65)
Fatigue	58/80 (73)	42/58 (72)
Stiff joints	50/80 (63)	23/50 (46)
Sore eyes	23/80 (29)	15/23 (63)
Wheeziness	17/80 (21)	7/17 (41)
Headache	40/80 (50)	27/40 (68)
Upset stomach	16/80 (20)	8/16 (50)
Sleeping problems	36/80 (45)	24/36 (67)
Dizziness	35/80 (44)	28/35 (80)
Loss of strength	50/80 (63)	40/50 (80)
Forgetfulness	48/80 (60)	39/48 (81)
Reading problems	21/80 (26)	16/21 (76)
Seeing problems	21/80 (26)	16/21 (76)
Speaking problems	23/80 (29)	23/23 (100)
Writing problems	18/80 (23)	15/18 (83)
Clumsiness	30/80 (38)	28/30 (93)
Tingling or numbness	36/80 (45)	29/36 (81)
Weakness	45/80 (56)	40/45 (89)
Paralysis	12/80 (15)	12/12 (100)
Upset or weepy	23/80 (29)	21/23 (91)

7.6.2 Description of illness representations

Table 7-6 shows the mean and standard deviations of the baseline illness perceptions domain scores in the study sample. Participants held strong beliefs about their personal ability to control their stroke symptoms, the ability of treatment to control stroke symptoms with 75-80% of participants reporting scores above the domain midline. Additionally, strong beliefs about the consequences of the stroke, and its emotional impact were also observed as half of the participants scored above the midpoint on theses domains.

Table 7-6 Mean and standard deviation of IPQ-R domains

IPQ-R Domain	Possible range of scores	n=76	
		Mean (SD)	Above median score
Identity	0-22	6.5 (5.0)	-
Timeline- acute/chronic	6-30	16.0 (4.3)	23%
Timeline- cyclical	4-20	11.3 (3.2)	33%
Consequences	6-30	18.6 (5.1)	50%
Personal control	6-30	21.1 (3.5)	80%
Treatment control	5-25	17.8 (3.0)	75%
Coherence	5-25	14.9 (3.8)	42%
Emotional	6-30	18.4 (5.0)	53%

The sample size was not sufficient (n<100) to conduct factor analysis to identify patterns of causal belief for stroke (e.g. lifestyle, environment, biomedical). Questions about causal beliefs were located in the last section of the IPQ-R questionnaire pack and item non-response was high. Between 5% and 10% of the individual questions about possible causes of stroke were left blank, and complete case data about causal factors was only available for 84% (n=67) of the study sample. Figure 7-5 shows the percent who agree or strongly agree that the various factors asked about were possible causes of stroke. Nearly half of the study sample thought that age was a possible cause. Additionally stress/ worry, and bad luck were endorsed by a third of respondents as factors they believed could have caused their stroke.

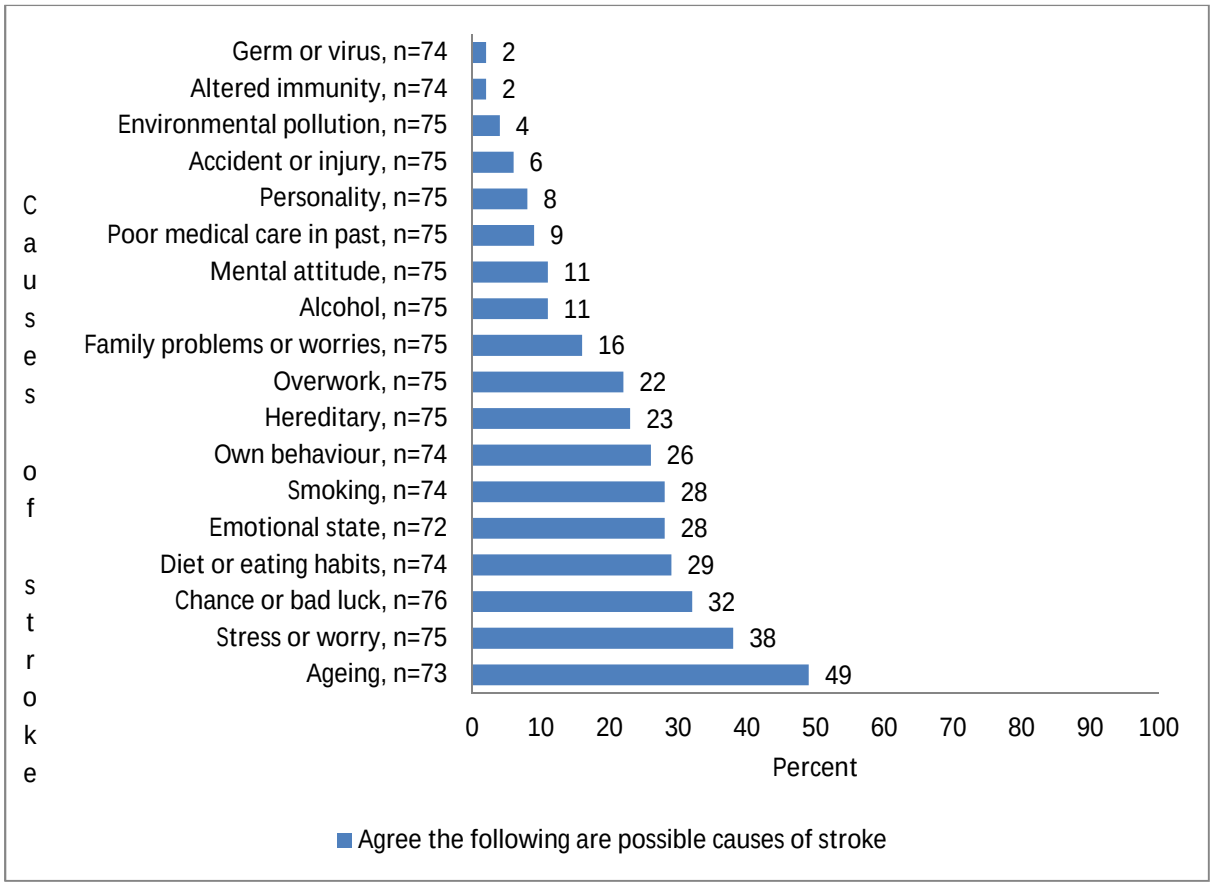


Figure 7-5 Causal attributions for stroke

7.7 Correlations between Illness Representations, Anxiety, Depression, Clinical, and Demographic variables at baseline

Bivariate Spearman's rank correlation coefficients (r_s) were calculated to assess the level of association between illness representation domains with each other, with anxiety and depression, and also with other clinical and demographic variables of interest (Table 7-7). These correlations were also used to identify statistical multicollinearity amongst predictor variables that would be entered in the regression model in section 7.9. Anxiety and depression were strongly correlated with each other (r_s= .71, p<.001), and the association between emotional representations and anxiety was also strong (r_s= .62, p<.001). Inter-relationships between illness representation domains were generally weak (i.e. r_s<.50), and supported some of the logical trends observed in previous research (Hagger and Orbell 2003). For example, identity had a significant positive correlation with the timeline and consequence domains, and was negatively, albeit non-significantly, associated with the personal and treatment control domains. Additionally, perceiving stroke to be more chronic (timeline), and unpredictable (cyclical) was positively and significantly correlated with perceptions about consequence.

Table 7-7 Correlation between clinical, demographic, and IPQ-R variables (n=76)

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	Age	1.00																		
2	HADS-A	-0.09																		
3	HADS-D	0.01	.71**																	
4	HADS-T	-0.04	.93**	.91**																
5	IR- Identity	-0.10	.58**	.63**	.66**															
6	IR- Timeline	-0.10	.34**	.35**	.37**	.56**														
7	IR-Cyclical	0.13	.34**	.35**	.37**	.51**	.33**													
8	IR-Consequence	-.27*	.44**	.43**	.47**	.53**	.41**	.29*												
9	IR-Personal Control	-0.05	-0.06	-0.12	-0.08	-0.13	-.32**	-.25*	0.10											
10	IR-Treatment control	0.13	-0.15	0.05	-0.05	-0.10	-.31**	-0.16	0.06	.44**										
11	IR-Coherence	-0.06	-.25*	-0.14	-0.21	-0.21	-0.12	-0.21	-0.10	.28*	0.16									
12	IR- Emotional	-0.06	.62**	.43**	.56**	.39**	.25*	.30**	.34**	-0.15	-0.21	-.32**								
13	Barthel Index	-0.13	-.26*	-.40**	-.36**	-.32**	-.25*	-.28*	-.35**	0.07	-0.04	0.03	-0.04							
14	6 CIT	0.16	0.18	.25*	.24*	0.18	0.22	.37**	0.16	-.29*	0.03	-0.12	0.07	-0.13						
15	Sex (female)	.25*	0.22	0.13	0.20	0.10	-0.01	0.17	-0.08	-0.10	-0.11	-0.03	0.01	-0.21	-0.04					
16	Living alone	0.13	0.04	0.22	0.13	0.14	-0.01	0.09	-0.01	0.04	0.12	-0.10	0.06	-0.13	0.21	0.03				
17	Comorbidities	.48**	0.17	0.21	0.21	0.07	0.08	.28*	0.02	-0.12	-0.09	-0.21	0.18	-0.06	0.20	.22*	0.15			
18	Stroke Type (Stroke)	0.09	0.13	.34**	.24*	.31**	0.16	-0.03	0.10	0.01	0.10	0.09	0.09	-0.09	-0.07	0.14	0.10	0.15		
19	Time post stroke (weeks)	0.04	0.15	.32**	.24*	.40**	.36**	0.20	0.04	0.02	0.03	0.10	0.05	-0.02	0.01	0.11	0.02	0.15	.36**	
20	Pre-stroke anx or dep (YES)	-0.05	.27*	.28*	.29*	0.12	0.01	0.12	0.04	-0.07	-0.06	-0.14	0.18	-0.04	0.10	0.10	0.13	0.06	0.00	0.06

IR- Illness Representation domain

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

7.8 Research Question 1: Are there any differences in illness representations between anxious and non-anxious stroke survivors at baseline?

Due to the high frequency of co-morbid anxiety and depression, it was determined that prior to testing a multivariate regression model for factors predictive of anxiety at baseline, a multivariate analysis of variance (MANOVA) test should be undertaken to determine whether there were differential patterns observed between those with anxiety, those with depression, or those with neither anxiety or depression, as having depression could result in a differential patterns of illness belief. For the MANOVA analysis the study sample was categorised into three groups:

1) No anxiety or depression (i.e. HADS-A and HADS-D score <11),

2) anxiety (i.e. HADS-A ≥11 and HADS-D not ≥11), and

3) depression (i.e. HADS-D≥11).

Individuals with co-morbid anxiety and depression were classified as depressed, in keeping with the hierarchical diagnostic nature of depression generally having priority over anxiety in clinical settings. Each of the individual IPQ-R domain scores were entered as dependent variables.

The MANOVA revealed a significant overall effect ($F[16, 134]=2.60$, $p=0.001$, partial $\varepsilon^2= 0.24$, power= 0.99) (Table 7-8). The Box-M test was non-significant (Box's M= 112.69, p=.19) indicating that the null hypothesis of equal covariance of the dependent variables across the groups, could not be rejected. Additionally, the Levene's tests for equality of variance were non-significant for each of the IPQ-R domain variables (Appendix I)

Findings from the MANOVA analysis showed there were some significant differences in patterns of illness representations between those defined as anxious or depressed relative to those without mental health distress. Post-hoc multiple comparison tests adjusted for multiple comparisons using the Bonferroni correction significance set to p<.01,

found that participants who were anxious viewed their stroke symptoms as less predictable (i.e. more cyclical) in nature (p=.03), as having a greater life consequence (p=.02), and they had a higher level of emotional response to their stroke (p=.01) relative to those without any mental health problems. However none of the mean IPQ-R domain scores were found to differ significantly between those defined as anxious or depressed (Table 7-8).

Table 7-8 MANOVA comparisons of the illness perceptions (IPQ-R) between anxious and non anxious patients

					MANOVA	
IPQ-R Domain	Possible range	None n=50 Mean (SD)	Anxiety n=12 Mean (SD)	Depression n=14 Mean (SD)	F	ε^2
Identity	0-22	4.9 (4.2)	8.7 (4.7)	10.9 (5.1)	11.12**	.23
Timeline	6-30	15.4 (4.1)	16.2 (4.0)	17.2 (5.4)	0.98	.03
Cyclical	4-20	10.7 (2.9)	13.3 (3.0)	11.9 (3.9)	3.87*	.10
Consequences	6-30	17.2 (4.9)	21.2 (3.9)	21.4 (5.0)	6.25**	.15
Personal Control	6-30	21.4 (3.8)	21.8 (2.9)	19.6 (2.8)	1.55	.04
Treatment control	5-25	17.8 (3.0)	17.9 (2.6)	17.8 (3.0)	0.04	.001
Coherence	5-25	15.7 (3.5)	13.3 (3.1)	13.9 (4.5)	2.82	.07
Emotional	6-30	17.0 (4.5)	21.8 (3.0)	20.3 (5.9)	6.78**	.16

*p<0.05, **p<0.01

7.8.1 Discriminant analysis for significant MANOVA

A discriminant function analysis was performed because the finding from the MANOVA was statistically significant. Discriminant function analysis (DA) supports a greater understanding of the data set by providing insight into the meaning of a significant MANOVA, and identifies the combination of score variables which led to the significant MANOVA. For the MANOVA analysis to work, predictor variables are entered as dependent variables. DA is essentially the reverse of MANOVA. This reversal of labelling is a consequence of the aim of MANOVA being to test differences between means, while the aim of discriminant function analysis is to assess whether members of different groups (i.e.

those with anxiety or depression) can be identified on the basis of their scores on a set of variables (i.e IPQ-R domains). DA also determines which of the independent variables account for most of the differences in the average score profiles of the respective groups.

The key assumptions for deriving the discriminant function are multivariate normality of the independent variables (this was observed in this sample), and unknown (but equal) dispersion and covariance matrices for the groups. When data do not meet the normality assumption there are problems in the estimation of the discriminant function, in which case logistic regression is suggested as an alternative. However the small sample size meant that logistic regression was inappropriate as the predictor to variable ratio would not be achieved. A minimum ratio of 10-20 observations for each predictor variable has been suggested for logistic regression, however as in this case, such a large sample size was not achievable. DA is also sensitive to the ratio of sample size to the number of predictor variables. However it has been determined in DA that the smallest group size just has to exceed the number of predictor variables in the equation. The smallest group size required from this study was 8 cases, making the sample size sufficient. The sample size requirement for logistic regression on the other hand is more stringent whereby the minimum number of cases is equal to: [10*(# of predictors)/ smallest of the proportions for dependent groups]. For such analysis a sample size of 445 would have been required.

10 * (8 IPQ variables)/ 0.18 the proportion with anxiety

In DA variable scores are combined in so that a single new composite variable, the discriminant score, is produced. A primary function of DA is to validate the likelihood that a respective observation will be correctly classified according to the derived discriminant function or to determine the most parsimonious way to distinguish between persons who vary on a given attribute of interest (e.g mental health status). Given the overlap between anxiety and depression, this could lend insight into what (if any) aspects are different between these two groups.

In most instances of DA the sample is divided into two subsamples, one used for estimating the discriminant function (the analysis sample), and the other for validation purposes (the holdout sample). This method of validating the discriminant functions is

referred to as the split-sample or cross validation approach. In the event the sample size is not large enough to split (i.e. n<100) then the compromise is to develop the discriminant functions on the entire sample and then use the functions to classify the same group used to develop the function. However a limitation of this approach is that it gives an inflated idea of the predictive accuracy of the function.

The DA was carried out to predict whether stroke participants would have anxiety, depression, or no mental health distress. Predictor variables were the eight IPQ-R domain scores. Significant mean differences were observed for identity, emotional, consequence and timeline cyclical domains (Table 7-10). The Box M test which assesses whether the variances across the dependent variable groups is similar was not significant (Box M= 112.69, F (72, 3019)=1.15, p=.19). In DA the number of discriminant function comparisons is always one less than the number of groups in the dependent variable. In this case two discriminant functions differentiated mental health status (anxiety vs depression vs none) and accounted for 78% and 22% of the variance respectively. The Wilks' lambda was statistically significant for the combined functions [X^2 (16)= 38.99, p=0.001], but was not significant when the first function was removed [X^2(7)= 9.50, p=0.22] (Table 7-9). This means that the two discriminant functions are statistically significant, however function 2 is not statistically significant on its own.

Table 7-9 Wilks' Lambda

Test of Function(s)	Wilks' Lambda	Chi-square	Df	Sig.
1 through 2	.57	38.99	16	.001
2	.87	9.50	7	.22

The standardised discriminant function coefficients are like that in multiple regression. Table 7-10 shows the importance of each predictor similar to the standardised regression coefficients in multiple regression. The sign indicates the direction of the relationship. The illness identity variable was the most highly correlated with function 1 at

(r=.75), followed by illness consequences (r=.57) and emotional representations (r=.55). These three variables stand out as those that strongly predict allocation to mental health status group (i.e. anxious, depressed or no mental health distress). The second function maximally distinguished the anxious group from the other two groups and loaded most strongly with the cyclical timeline score (r=.46). Function 2 also distinguished the depressed group from the other two groups and on the personal control domain (r=.42). The F values in Table 7-10 were only significant for some of the illness representation domains, indicating the mean scores on theses variables were not significantly different across the three groups.

Table 7-10 Results of discriminant analysis of predictors associated with anxiety or depression in stroke patients at baseline (n=76)

Predictors	Standardised discriminant function coefficient (Pearson correlations)		F (2, 73)
	Function 1	Function 2	
Identity	.72 (.75)	-.65 (-.18)	11.12***
Consequence	-.40 (.57)	.02 (.12)	6.25**
Emotional	-.05 (.55)	.72 (.41)	6.78**
Coherence	.40 (-.36)	.01 (-.24)	2.82
Timeline (acute/ chronic)	-.33 (.22)	.73 (-.13)	.98
Treatment control	.31 (.05)	-.04 (-.01)	.04
Timeline (cyclical)	-.18 (.38)	-.31 (.46)	3.87*
Personal control	.37 (-.18)	.41 (.42)	1.55

*p<0.05, **p<0.01, ***p<0.001

Unstandardised discriminant function coefficients are used to create the discriminant function equation and it operates like a regression equation. In this case it is:

$D_{(function\ 1)}$=(.16*Identity)-(.09*Timeline)-(.02 * cyclical)+(.08*consequence)-(.09*Personal)+.10*Treatment)-(.05*Coherence)+.(08*Emotional)-1.53

$D_{(Function\ 2)}$= -(.14*Identity)+(.01*Timeline)+(.23*cyclical)+(.001*consequence)+(.21*personal)-(.01*Treatment)-(.08*Coherence)+(.09*Emotional)-6.269

These equations indicated the partial contribution of each variable to the discriminate function controlling for all other variables in the equation. They can be used to assess each predictors unique contribution to the discriminant function and provide information on the relative importance of each variable.

The last step in evaluating the DA is to describe each group in terms of its profile using the group means of the predictor variables. These group means are called centroids. In this study, on function 1 those with no mental health distress had a mean of -.50, those with anxiety a mean of .79, and those with depression 1.13 (Table 7-11).

Table 7-11 Functions at group centroids table

Groups	Function 1	Function 2
No mental health distress	-.50	-.04
Anxiety	.79	.75
Depression	1.13	-.51

This analysis is displayed graphically in (Figure 7-6 & Figure 7-7). The boxplots of function 1 show that there is substantial overlap between anxiety and depression, but less in comparison to those with neither anxiety or depression. Function 2, which is not significant in the absence of function 1, shows that the differentiation between anxiety and depression improves, but there is substantial overlap between those with depression and no mental health distress.

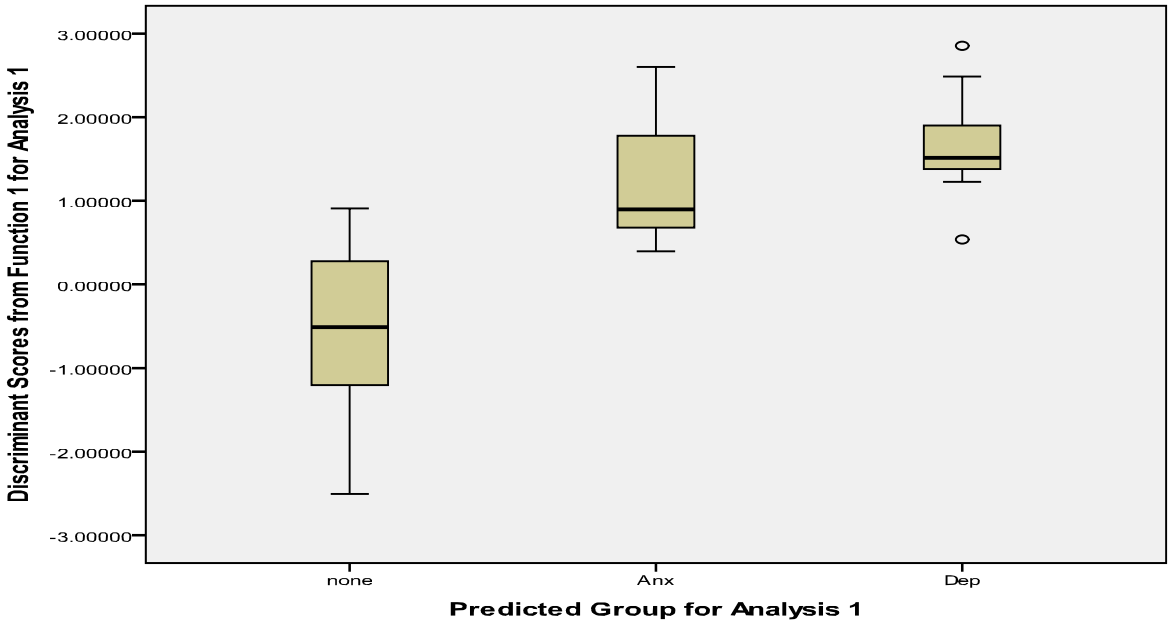


Figure 7-6 Box plot illustrating the distribution of function 1 discriminant scores by group

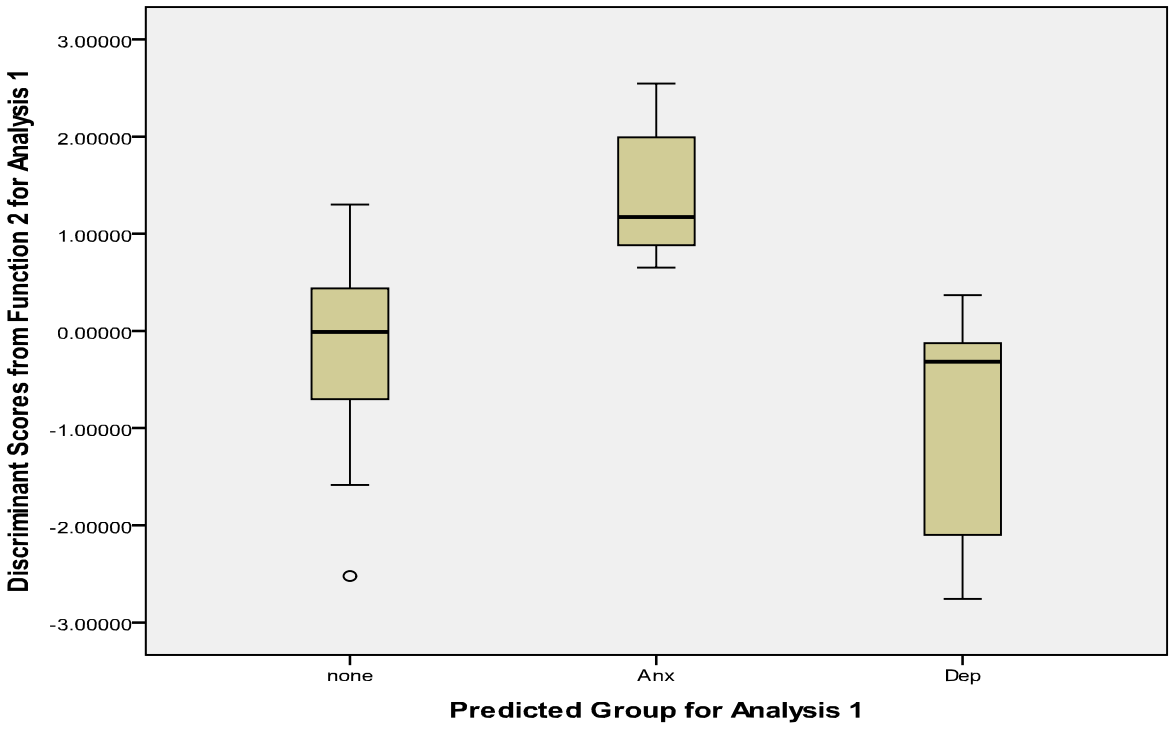


Figure 7-7 Box plot illustrating the distribution of function 2 discriminant scores by group

The discriminant analysis based on these data did not differentiate between individuals defined as anxious or depressed. This was confirmed by the findings from the classification results, whereby only 60% of the cross-validated grouped samples were correctly classified (Table 7-12). Correct classification of those without mental health distress was high (82%), whereas correct classification of patients with either anxiety or depression was much less accurate at 8% for those defined as anxious and 29% for those defined as depressed. This is less than the 33.3% that would be expected by chance alone. These findings support the notion that those defined as anxious did not differ statistically from those defined as depressed in this study sample. All subsequent analyses were conducted with anxiety as the outcome of interest, with adjustment made for depression scores.

Table 7-12 Discriminant analysis classification table results

Classification Results[b,c]					
	Occurrence of Emotional Distress	Predicted Group Membership N (%)			
		None	Anxious	Depressed	TOTAL
ORIGINAL	None	43 (86.0)	5 (10.0)	2 (4.0)	50
	Anxious	6 (50.0)	4 (33.3)	2 (16.7)	12
	Depressed	6(42.9)	2 (14.3)	6 (42.9)	14
CROSS-VALIDATED	None	41 (82.0)	5 (10.0)	4 (8.0)	50
	Anxious	8 (66.7)	1 (8.3)	3 (25.0)	12
	Depressed	7 (50.0)	3 (21.4)	4 (28.6)	14

* Cross validation is done only for those cases in the analysis. In cross validation, each case is classified by the functions derived from all cases other than that case.
b. 69.7% of original group cases correctly classified
c. 60.5% of cross-validated group cases correctly classified

7.9 Research Question 2: Are illness representations at baseline associated with anxiety levels at baseline?

Hierarchical multiple regression analysis was conducted to examine the extent to which illness representations and other potentially relevant variables predicted baseline anxiety score. Age, sex, the Barthel index and pre-stroke history of mental health problems (i.e. anxiety or depression) were entered in the first block, cognitive illness representations were entered in the second block, and the emotional representation domain in the third block (Table 7-13).

In the first block baseline score on the Barthel index (β= -.38, p=0.02) and having a pre-stroke history of anxiety or depression (β=2.70, p=0.03) were significant predictors of anxiety. The variables entered into the model at this step explained 16% of variance in anxiety scores. Once cognitive representations were entered into the model, illness identity was the only variable found to be a significant predictor of anxiety (β=.35, p=0.004). Baseline Barthel score, and pre-stroke history of anxiety or depression were no longer significant predictors of anxiety at this stage. The proportion of variance explained by the model increased significantly to 36%. The final step involved including emotional representation into the regression model. Emotional perception of stroke was a significant predictor of anxiety score (β =.40, p<.001) and illness identity representations remained the only other variable that was a significant predictor of anxiety score (β =.29, p=.01). Overall, the final model explained 49% of the variance in anxiety scores.

Muliticollinearity amongst predictors was within acceptable levels as the variance inflation factor (VIF) did not exceed 5 for any of the variables in the model. A histogram of the regression standardised residuals show that they were normally distributed. This was confirmed statistically by a non-significant Shapiro-Wilk test (W=.98, df=76, p=.41). Inspection of the normal probability plot showed that the residuals met the assumption of linearity, while a scatter plot of standardised residuals versus predicted residuals indicated there was constant variance across each level of the predicted value (i.e. homoscedasticity). There were no outliers amongst the standardised residuals as none had a value >3. Finally, there were no observations exercising undue influence on the regression coefficients as

none had a leverage value greater than the critical value of 0.513. The regression diagnostic plots are in Appendix I.

Table 7-13 Regression analysis predicting anxiety at baseline

Step	Variables	Unstandardized Coefficients B	Standardized Coefficients Beta	t	Sig.	R^2	Adjusted R^2	F change in R^2
1	(Constant)	16.207		4.01	<.001	.20	.16	4.45**
	Barthel Index	-.38	-.27	-2.48	.02			
	Pre-stroke anx or dep [YES]	2.7	.23	2.16	.03			
	Age	-.05	-.14	-1.30	.20			
	Female	1.47	.17	1.51	.14			
2	(Constant)	2.77		.43	.67	.46	.36	4.33**
	Barthel Index	-.03	-.04	-.22	.83			
	Pre-stroke anx or dep [YES]	1.89	.19	1.67	.10			
	Age	-.002	-.03	-.05	.96			
	Female	1.45	.17	1.61	.11			
	Identity	.36	.38	3.00	.004			
	Timeline	.02	.02	.17	.87			
	Cyclical	-.03	-.03	-.17	.87			
	Consequence	.21	.21	1.78	.08			
	Personal	.06	.05	.45	.66			
	Treatment	-.11	-.06	-.61	.54			
	Coherence	-.19	-.14	-1.49	.14			
3	(Constant)	-2.48		-.41	.68	.58	.49	17.01***
	Barthel Index	-.03	-.09	-.21	.83			
	Pre-stroke anx or dep [YES]	1.43	.15	1.41	.16			
	Age	-.01	-.04	-.18	.86			
	Female	1.45	.17	1.81	.08			
	Identity	.30	.32	2.77	.01			
	Timeline	.04	.03	.33	.74			
	Cyclical	-.10	-.08	-.69	.49			
	Consequence	.10	.09	.91	.37			
	Personal	.07	.05	.53	.60			
	Treatment	.06	.04	.35	.73			
	Coherence	-.07	-.05	-.63	.53			
	Emotional	.40	.43	4.21	<.001			

**p<.01, ***p<.001

7.10 Summary of findings at baseline

- There was little difference observed between responders and non-responders with the exception that the latter had significantly higher cognitive impairment screening scores than former. Otherwise the two groups did not differ significantly on any other variable.
- The study sample had low levels of residual impairment in activities of daily living and cognitive impairment.
- One third of study participants were found to be anxious at baseline and of these, 42% also had co-morbid depression. Furthermore, anxiety symptom severity scores were significantly higher than depression symptom severity scores.
- Having depression in addition to anxiety did not result in differential illness representation scores.
- After adjusting for age, sex, history of anxiety or depression, and baseline Barthel index score, illness identity and emotional representations were the only two domains of illness representation found to be significantly associated with anxiety at baseline. The regression model explained 49% of the variance in anxiety scores

8 Chapter Eight: Study 3- Results Longitudinal analysis

8.1 Introduction

The following chapter extends upon results that were reported in the chapter seven baseline cross-sectional analysis. The population lost to follow-up is described. A cluster analysis used to identify overall illness schema, and for data reduction is explained. Changes in the level of anxiety, and illness representations were examined. Linear regression and structural equation models developed to predict anxiety at follow-up are presented. Changes in the causal attribution of stroke over time were also examined.

8.2 Study population at follow-up

Eighteen (22%) individuals were lost to follow-up at time two. Additionally, three (5%) participants indicated they had experienced a recurrent stroke. Longitudinal analysis was conducted for 62 participants with data available from both time points.

A series of univariate tests were conducted to identify differences between those lost-to follow-up, and those who returned questionnaires at time two (Table 8-1). Those lost to follow-up had significantly higher baseline depression, and greater impairment on activities of daily living relative to those who returned the follow-up questionnaires. There was no significant difference observed between the groups on baseline illness representations or on any other factor assessed.

The level of impairment in activities of daily living remained constant. There was no significant change on the median Barthel index score from baseline to follow (18, IQR 15-20 vs. 19, IQR 15-20, W=.18, p=0.86).

Table 8-1 Comparison between participants lost to follow-up and those responding at time two

	Lost to follow-up n=18	Returned Time 2 data n=62	Significance
Age in years			U=436, p=.16
Median	64.5	73	
<65 years: n(%)	9 (50)	13 (21)	
Sex: n(%)			X^2=.17, p=.79
Female	8 (44)	31 (50)	
Male	10 (56)	31 (50)	
Live Alone: n(%)			X^2= .27, p=.60
No	11 (61)	42 (68)	
Yes	7 (39)	20 (32)	
Type of Stroke: n(%)			X^2= .01, p=.91
Cerebral Infarction	11 (61)	37 (60)	
TIA	7 (39)	25 (40)	
6CIT			U=442, p=.40
Median	4	6	
History of anxiety or depression: n(%)			Fisher exact p= 1.00
No	15 (83)	50 (81)	
Yes	3 (17)	12 (19)	
Smoking status: n(%)			U=393, p=.10
No	16 (88)	45 (73)	
Yes	1 (6)	12 (19)	
Ex-smoker	1 (6)	5 (8)	
Number of co-morbidities: n(%)			U=483, p=.35
0	9 (50)	23 (37)	
1	6 (33)	25 (40)	
2	2 (11)	10 (16)	
3	1 (6)	4 (7)	
Time post-stroke at recruitment (weeks)			U=415, p=.10
Median	6	7.5	
Recruitment location: n(%)			Fisher exact p=.76
Barnsley	13 (72)	47 (76)	
Sheffield	5 (28)	15 (24)	
HADS score: mean (sd)			
Anxiety subscale	8.2 (4.8)	6.8 (4.5)	t(78)= 1.14, p=.26
Depression subscale	8.7 (4.8)	5.7 (3.9)	t(78)=2.44, p=.02
Barthel Index			
median	15.5	18.0	U=332, p=.01
Illness representations at baseline:			
Mean (SD)			
Identity	7.6 (6.2)	6.1 (4.6)	t (78)= 1.11, p=.27
Timeline (acute/ chronic)	15.6 (4.0)	16.1 (4.4)	t(76)=-.48, p=.63
Timeline (cyclical)	12.1 (2.7)	11.1 (3.3)	t(76)= 1.06, p=.29
Consequence	20.8 (4.5)	18.0 (5.1)	t(76)=2.13, p=.04†
Personal control	20.8 (4.6)	19.0 (4.8)	t(76)=-.44, p=.66
Treatment control	17.7 (3.7)	17.8 (2.8)	t(76)= -.11, p=.91
Coherence	14.6 (4.8)	15.0 (3.5)	t(76)= -.36, p=.72
Emotional	19.1 (6.0)	18.2 (4.6)	t(76)= .67, p=.50

U- Mann Whitney test, X^2- Chi-square, †-not significant after Bonferroni correction for multiple testing

8.3 Research Question 3: Does the prevalence of anxiety and anxiety symptom severity change over time?

The mean HADS-A score was 7.3 (SD= 4.9) at three month follow-up. Figure 8-1 shows that overall anxiety scores increased by 0.6 (SD= 3.9) from baseline, however this increase was not statistically significant (t=1.20, df=59, p=.23). The range of anxiety change scores ranged from -11 to +13. The mean HADS-D score was 5.5 (SD= 4.0) at three month follow-up. Mean depression scores decreased by -0.2 (SD= 3.5), but this decrease was not statistically significant (t=-.34, df= 59, p=.74). Depression change scores ranged from -9 to 10 between baseline and follow-up.

Table 8-2 shows that overall the proportion of stroke survivors with anxiety (HADS-A ≥11) was unchanged at follow-up compared to baseline (28% vs. 27%, W= -.26, p=.80). Of the 43 participants with no mental health distress at baseline, 7 (16%) were found to be anxious at follow-up. Five of these individuals were defined as anxious only, while two had co-morbid anxiety and depression. The baseline HADS-A scores of these newly anxious individuals, was 8 or 9 for six of the seven individuals. One person who was anxious at follow-up had a baseline HADS-A score of zero. The baseline depression scores for these newly anxious individuals was more varied in that HADS-D scores ranged from 0-9 with no clear pattern emerging.

Of the 16 participants who had anxiety at baseline (i.e. anxiety only or co-morbid anxiety and depression), 9 (56%) remained anxious at three month follow-up (Table 8-2). Anxiety symptom severity was significantly higher amongst those with anxiety at baseline and follow-up. Their mean anxiety level at baseline was 12.67, SD=2.1 (t=7.11, p<.001) and increased to 14.44, SD=3.1 (t=7.06, p<.001) three months later.

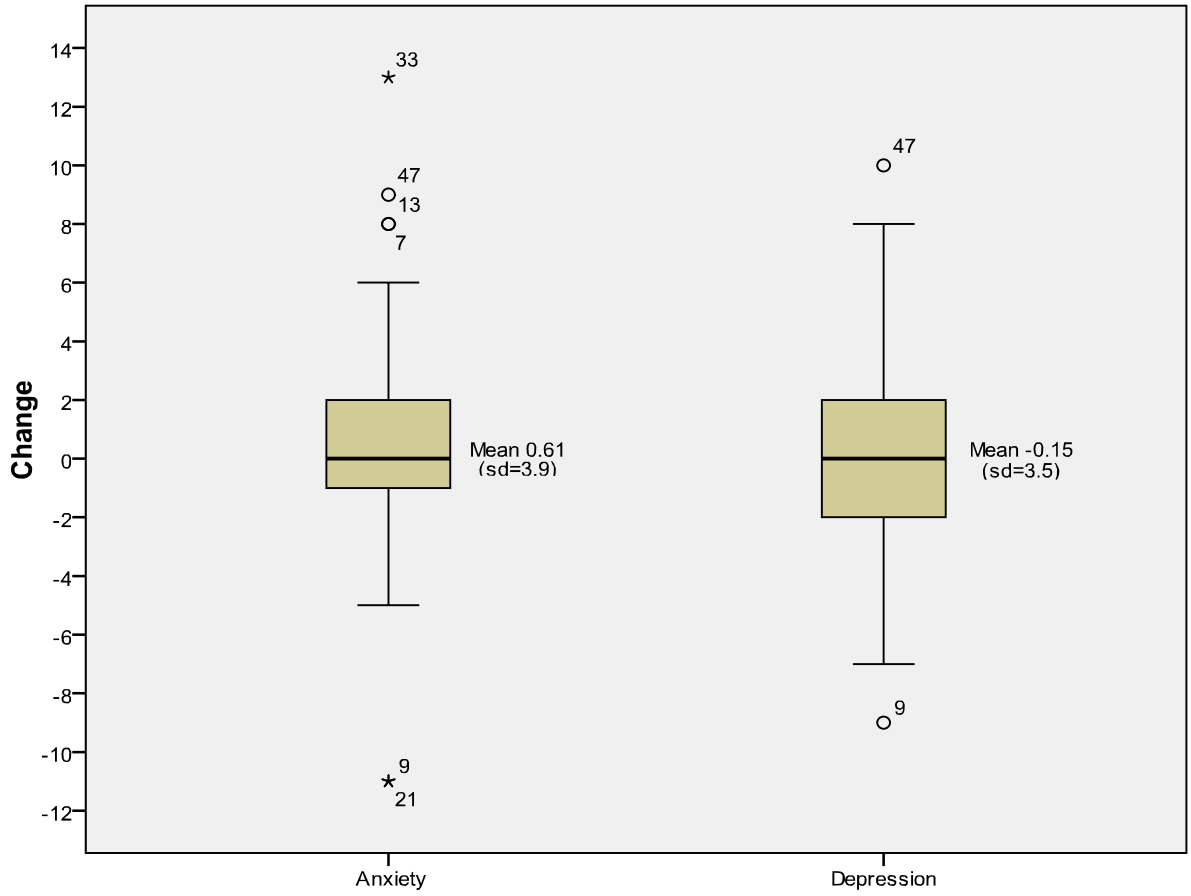


Figure 8-1 Anxiety and depression change scores from baseline to 3-month follow-up

Table 8-2 Number (%) of participants who had anxiety and/or depression at baseline and 3 month follow-up

	Mental Health Status at Baseline				
Mental Health Status at follow-up	No anxiety or depression	Anxiety	Depression	Anxiety & Depression	TOTAL
No anxiety or depression	36 (84)	3 (30)	-	4 (67)	43 (72)
Anxiety	5 (12)	4 (40)	-	-	9 (15)
Anxiety & Depression	2 (4)	3 (30)	1 (100)	2 (33)	8 (13)
TOTAL	43	10	1	6	60

8.4 Research Question 4: Do stroke survivors change their illness representations over time?

The following section tests the hypothesis that stroke survivors do not self-regulate their illness beliefs and no change in illness representations would be observed between baseline and three month follow-up.

8.4.1 Change in Illness Representation domains over time

A repeated measures multivariate analyses of variance (MANOVA) showed that on the combined illness representation variables, change over time did not reach statistical significance,[F (8, 44)= 1.49, p=.19, Pillai's Trace= .214, partial ε^2= 0.19]. This was supported by paired t-test that showed that with the exception of treatment control and personal control cognitions, there was no significant change in individual illness representations between baseline and follow-up (Table 8-3). Over time participants views became more negative about the ability of personal actions or treatment to have an impact on their stroke symptoms.

Table 8-3 Change in illness perceptions between baseline and 3-month follow-up (n=62)

Illness Perceptions	Range	Baseline Mean (SD)	Follow-up Mean (SD)	Mean Difference	t	Sig
Identity	0-22	6.3 (4.6)	6.5 (4.7)	0.2	.57	.57
Timeline	6-30	16.1 (4.4)	16.8 (4.8)	0.7	1.25	.22
Cyclical	4-20	11.1 (3.3)	10.8 (3.1)	-0.3	-.87	.39
Consequence	6-30	17.9 (5.1)	17.8 (5.0)	-0.1	-.19	.85
Personal	6-30	21.2 (3.5)	20.0 (2.8)	-1.2	-2.54	.01
Treatment	5-25	17.8 (2.8)	16.3 (3.2)	-1.5	-3.15	.003
Coherence	5-25	15.0 (3.5)	15.0 (3.7)	0.02	.18	.86
Emotional	6-30	18.2 (4.6)	18.1 (4.4)	-0.1	-.20	.84

8.4.2 Change in causal beliefs

McNemar test of paired proportions found that causal beliefs remained constant over time, as no significant change from baseline was observed for any of the items at follow-up (Table 8-4). Age, stress, and chance or bad luck remained the items that participants endorsed most frequently as possible causes of stroke.

Table 8-4 Proportion of participants who agreed or strongly agreed item is a possible cause of stroke

	% who agree item is possible cause of stroke at follow-up (n=62)	% Change from Baseline	Sig.
Stress	47.5	25.0	.31
Hereditary	23.7	3.0	.57
Germ or virus	5.1	155.0	.68
Poor diet	26.3	-9.3	.91
Chance or bad luck	33.9	5.9	.95
Poor medical care in past	8.5	-5.6	.88
Pollution in environment	5.1	27.5	.68
Own behaviour	26.7	2.7	.06
Mental attitude	5.4	-50.9	.75
Family problems or worries	17.2	7.5	.51
Overwork	23.7	7.7	.75
Emotional state	26.7	-4.6	.29
Ageing	58.7	19.8	.07
Alcohol	13.3	20.9	.23
Smoking	23.7	-16.8	.96
Accident or injury	5.1	-16.7	.43
Personality	5.1	-37.5	.74
Altered immunity	5.1	155.0	.68

8.4.3 Illness representation clusters

Cluster analysis is a descriptive technique used to identify groups of similar people. Within the context of illness representations, it would take into account an individuals entire illness schema and identify groups of people that shared similar illness beliefs. It would also provide a major practical advantage for regression analyses designed to predict anxiety at follow-up. Using cluster analysis as a grouping mechanism reduced eight individual domain scores into one variable, and ensured that the regression model would not be oversaturated. The method of cluster analysis used has been validated in research into illness representations and long-term conditions (Clatworthy *et al.* 2007) and is described below.

8.4.3.1 Cluster analysis methodology for illness perceptions

To start simple change scores (follow-up score minus baseline score) of each of the eight IPQ-R domains were calculated. All change scores were then standardised to z scores prior to clustering. The number of groups that will emerge from a cluster analysis in a study sample is generally not known beforehand. A two stage process of analysis was conducted. Ward's method was used to determine the number of clusters, and this was followed by k-means clustering.

Each individual in the data set is assumed to be a separate cluster (i.e. there are as many clusters as cases). Statistical software then combines clusters sequentially, hence reducing the number of clusters at each step until only one cluster is left. The clustering method uses the dissimilarities or distances between objects when forming the clusters. A hierarchical tree called a dendrogram, is produced to show the linkage points and the clusters are linked at increasing levels of dissimilarity. The goal of the clustering algorithm is to join objects together into successively larger clusters, using a measure of similarity or distance. As a result, more and more objects are linked together and join larger and larger clusters of increasingly dissimilar elements. In the last step, all objects are merged together as one cluster. For each node in the graph, where a new cluster is formed, a criterion distance can be read, at which the respective elements are linked together into a new single cluster.

The squared Euclidean distance is the most straightforward and generally accepted way of computing distances between objects. The Ward method is the most commonly used method of measuring these distances. This method is distinct from other methods in that it uses an analysis of variance approach to evaluate the distances between clusters and is generally very efficient. Cluster membership is assessed by calculating the total sum of squared deviations from the mean of a cluster. The criterion for fusion is that it should produce the smallest possible increase in the error sum of squares.

The Ward method is good for getting a sense of the total possible number of clusters and the way they merge, as seen from the dendrogram. The second step is to validate the findings from the Ward method, by k-means clustering. K-means clustering can be viewed as a validation of the findings from the Ward method. At this stage a chosen number of clusters can be requested, and all cases will be placed in one of the clusters (i.e. k-means clustering).

8.4.3.2 Determining number of clusters

Standardised change scores from all eight domains were included for analysis. The Ward method produced an agglomeration schedule table to assist in selecting the ideal number of clusters in the data (Table 8-5). The raw SPSS output provides a solution of every possible number of clusters (or number of cases in the data set). The table presented is a re-formatted abridged version of SPSS output. The two columns in the middle provide coefficient estimates at a given level of clusters, and what the coefficient estimate would be at the next level of cluster. The 'change' column is used to determine the optimum number of clusters. In this dataset two clusters appear to be most appropriate, as it is at this point where there is a clear demarcation in the change in coefficient value. The dendogram supports the agglomeration table in that it shows two clear clusters (Figure 8-2). The K-means clustering selecting for two clusters was run to produce two clusters.

Table 8-5 Re-formed agglomeration table

No. of Clusters	Agglomeration last step	Coefficient at this step	Change
2	406.403	336.005	70.40
3	336.005	299.477	36.53
4	299.477	271.672	27.81
5	271.672	246.019	25.65
6	246.019	222.099	23.92
7	222.099	202.893	19.21
8	202.893	187.600	15.29
9	187.600	173.492	14.11

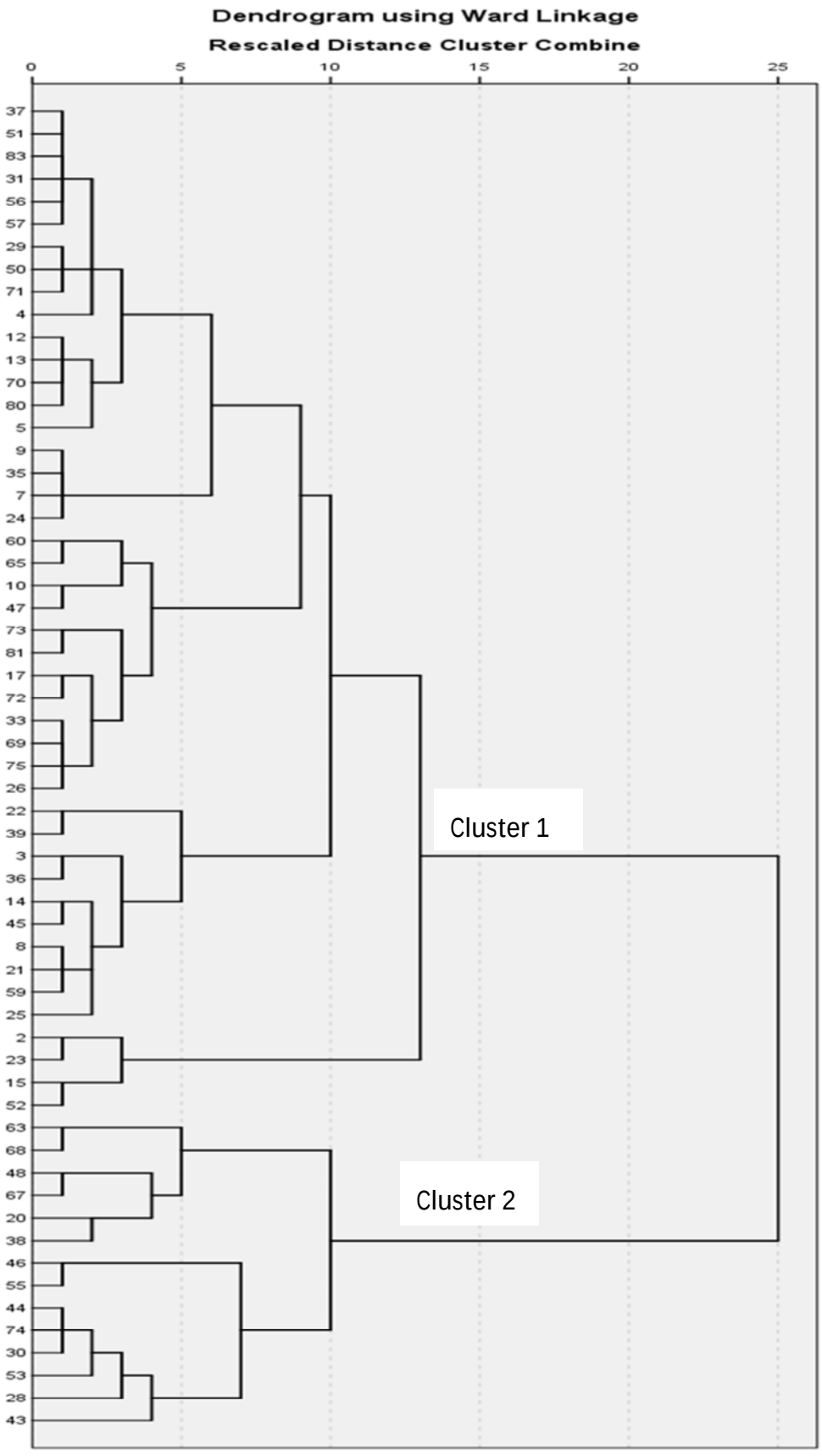


Figure 8-2 Dendogram after two-stage cluster process

Analysis revealed that individuals in cluster one generally held more negative representations about their stroke than those in cluster two. The mean number of symptoms attributed to stroke increased, as did perceptions about illness chronicity, unpredictability of symptoms, and consequences for those in cluster one. The opposite trend was observed for those in the positive cluster, and the difference between the two groups was statistically significant on these six illness representation domains. Those in cluster one did not differ significantly from those in cluster two on how they understood their stroke symptoms. Lastly, those in the negative group reported their stroke elicited less of an emotional response, while those in the positive cluster indicated an increase. The difference in coherence, and emotional representations were not significantly different between the two clusters (Table 8-6).

Table 8-6 Mean change in IPQ-R domain score, mood, and Barthel Index stratified by illness cluster

	Negative (Cluster 1) Mean (SD) n=45	Positive (Cluster 2) Mean (SD) n=14	F	Sig
IPQ-R domains				
Identity	0.9 (3.0)	-2.1 (3.9)	9.38	.003
Timeline	2.1 (3.2)	-3.6 (3.8)	31.13	<.001
Cyclical	0.4 (2.6)	-2.8 (3.4)	13.27	.001
Consequence	0.8 (3.3)	-3.1 (4.8)	11.79	.001
Personal	-2.0 (3.1)	1.1 (3.0)	10.54	.002
Treatment	-2.3 (2.9)	.93 (3.5)	12.38	.001
Coherence	0.01 (3.9)	-0.1 (3.2)	.01	.93
Emotional	-0.4 (3.5)	.90 (4.9)	1.27	.27

The mean anxiety scores decreased over time for those in the positive cluster, while they increased for those in the negative cluster, however the difference between the two clusters was not statistically significant (-0.50 sd=3.1 vs. 0.97 sd=4.3, $F(1,56)=1.44$, $p=.24$) (Figure 8-3). The mean depression scores also decreased for those in the positive cluster, however were unchanged for those in the negative cluster. The difference in depression scores was not significantly different between the two clusters (0.001 sd=3.7 vs. -0.85 sd=3.0, $F(1,56)=.63$, $p=.43$) (Figure 8-4). Analysis also showed that the proportion of

individuals with anxiety (HADS-A ≥11) was greater in the negative cluster compared to the positive cluster (68% vs. 30%, Fisher exact test, p=0.09), but the difference was not significant.

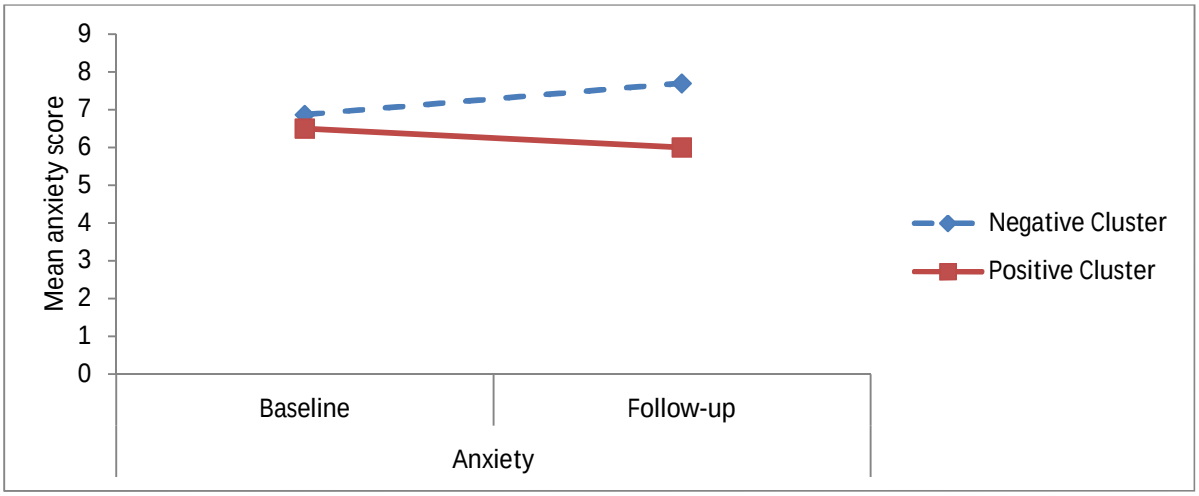


Figure 8-3 Mean anxiety score at baseline and follow-up stratified by cluster

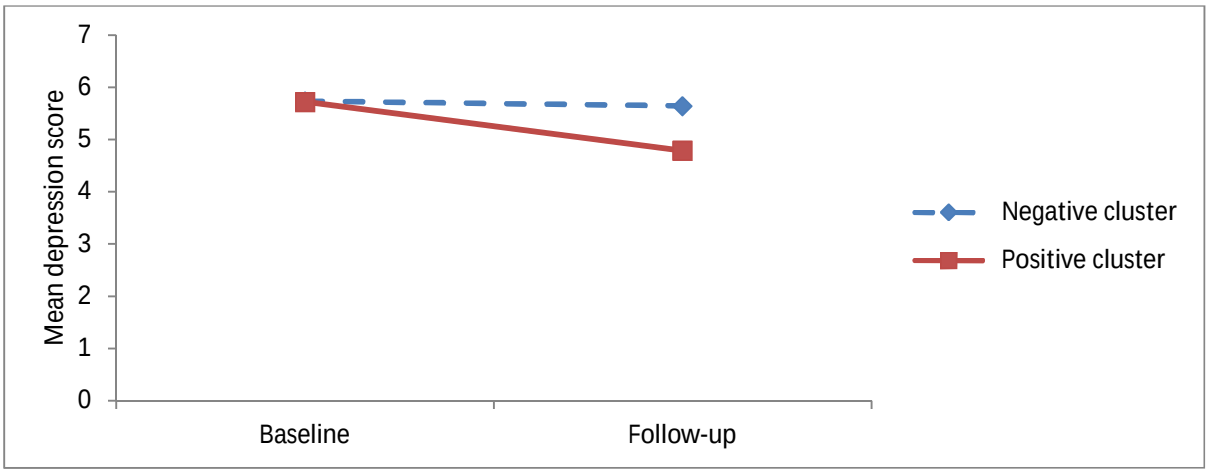


Figure 8-4 Mean depression scores at baseline and follow-up stratified by cluster

8.5 Research Question 5: Do illness representations predict anxiety at follow-up?

The following section presents the regression analyses that were conducted to determine whether illness representations predicted anxiety after stroke at follow-up.

Hierarchical multiple regression analysis was conducted to examine whether age, gender, having a history of anxiety or depression, impairment in activities of daily living, illness representation cluster, and anxiety at baseline predicted anxiety at three month follow-up.

In the first step none of the five variables (age, sex, pre-stroke history of anxiety or depression, Barthel index score, illness representation cluster) that were entered into the model were significant predictors of anxiety at follow-up. These five variables explained 9% of the variance in anxiety score at follow-up. Only anxiety at baseline (β=.62, p<.001) was a significant predictor of anxiety at follow-up (Table 8-7).

Table 8-7 Regression analysis predicting anxiety at follow-up

Step	Variables	Unstandardised coefficient B	Standardised coefficient Beta	t	Sig	Adjusted R^2	F change in R^2
1	Constant	14.11		2.20	.03	.09	2.59*
	Age	-.08	-.24	-1.33	.19		
	Female	1.32	.15	.99	.33		
	Prestroke anx or dep	3.23	.30	1.92	.06		
	Barthel T2	-.19	-.07	-.82	.42		
	Negative cluster	1.2	.08	.81	.42		
2	Constant	8.12		1.49	.14	.38	8.02**
	Age	-.05	-.15	-1.07	.29		
	Female	.37	.04	.33	.75		
	Prestroke anx or dep	1.30	.16	.90	.37		
	Barthel T2	-.15	-.01	-.79	.44		
	Negative cluster	1.33	.09	1.09	.28		
	Anxiety (Baseline)	.62	.58	5.00	<.001		

*p<.05, **p<.001

Multicollinearity amongst predictors was within acceptable levels as the variance inflation factor did not exceed 1.45 for any of the variables in the model. A histogram of the regression standardised residuals show that they were normally distributed. This was confirmed statistically by a non-significant Shapiro-Wilk test (W=.97, df= 56, p=.20). Inspection of the normal probability plot showed that the residuals met the assumption of linearity, while a scatter plot of standardised residuals versus predicted residuals indicated there was constant variance across each level of the predicted value (i.e. homoscedasticity). There also were no outliers amongst the standardised residuals as none had a value >3.

8.5.1 Structural Equation Modelling

A structural equation model (SEM) to predict anxiety at follow-up was carried out. A direct path between illness representation cluster, baseline barthel index score, baseline level anxiety, depression, and history of anxiety or depression was specified. A direct path between barthel score and illness cluster was specified, as were direct paths between barthel index score, and history of mental health problems with baseline anxiety and depression. An autocorrelation effect was specified between baseline anxiety and baseline depression.

Several fit indices were assessed to determine model fit. The chi-square tests the hypothesis that the model fits the data, in which case non-significance is indicative of good model fit. The chi-square test is sensitive to sample size, therefore three additional fit indices were examined. The comparative fit index (CFI)and the normative fit index (NFI) have values ranging from 0 to 1 and a general rule of thumb is that values larger than 0.90-0.95 are indicative of good fit (Blunch 2008). The Tucker Lewis index (TLI) was also examined, and values greater than 0.95 are considered acceptable. The root mean square error approximation (RMSEA) is another indicator of fit. By convention RMSEA ≤.05 refers to close fit, ≤.08 mediocre fit, and >.10 poor fit (Kelley and Lai 2011). The Akaike's Information Criterion (AIC) is the final of the fit indices. While not a specific measure of fit, it can help with model selection.

Two models are presented. The first (full) model showed that chi-square was not significant (X^2= 13.47, df=14, p=.49) supporting the hypothesis that the model fits the data could not be rejected. Other fit indices supported the chi-square findings (CFI= 1.00, TLI= 1.02, NFI= .89. The Root Mean Square error approximation (RMSEA) was 0.001(90%CI 0-.12, p=.63). The Akaike's Information Criterion (AIC) was 73.47. After taking into account autocorrelation between anxiety and depression (r=.75), baseline anxiety was the only significant predictor of anxiety at follow-up, with the model explaining 43% of the variance of anxiety scores at follow-up (Table 8-8 and Figure 8-5).

Model trimming was carried out by removing the non-significant paths from the model depicted in Figure 8-6. Fit indices show that the trimmed (simpler) model did not improve model fit: [X^2= 21.08, df=22, p=.52], CFI=1.00, TLI= 1.02, NFI= .83. The RMSEA= .001 (90%CI 0-.10, p=.68), AIC= 65.08.

Overall the SEM found that anxiety at baseline was the only significant predictor of anxiety at follow-up.

Table 8-8 SEM- Full Model and trimmed model predicting Anxiety at follow-up

	Unstandardized (SE)	Standardized	Sig	R^2
Full Model				.43
Baseline barthel index	.09 (.21)	.05	.65	
Age	-.05 (.04)	-.11	.29	
Sex (female)	.78 (.96)	.08	.41	
History of mental health problem	1.27 (1.3)	.10	.32	
Negative cluster	1.22 (1.1)	.11	.28	
Baseline Anxiety	.64 (.12)	.60	<.001	
Trimmed Model				.42
Illness perception cluster over time	1.55 (1.2)	.14	.18	
Baseline Anxiety	.69 (.11)	.63	<.001	

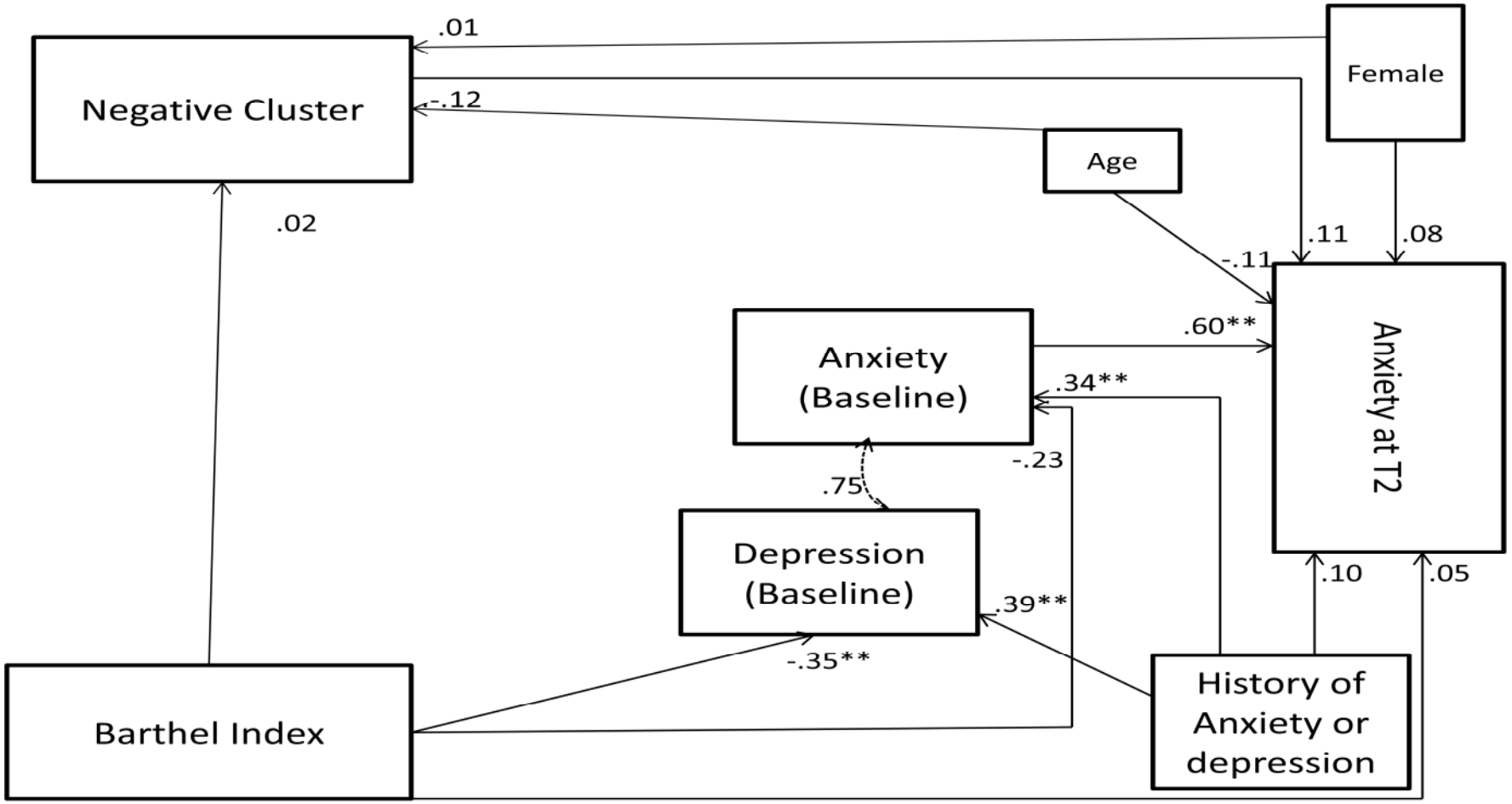


Figure 8-5 SEM Full Model

*p<.05, **p<.01

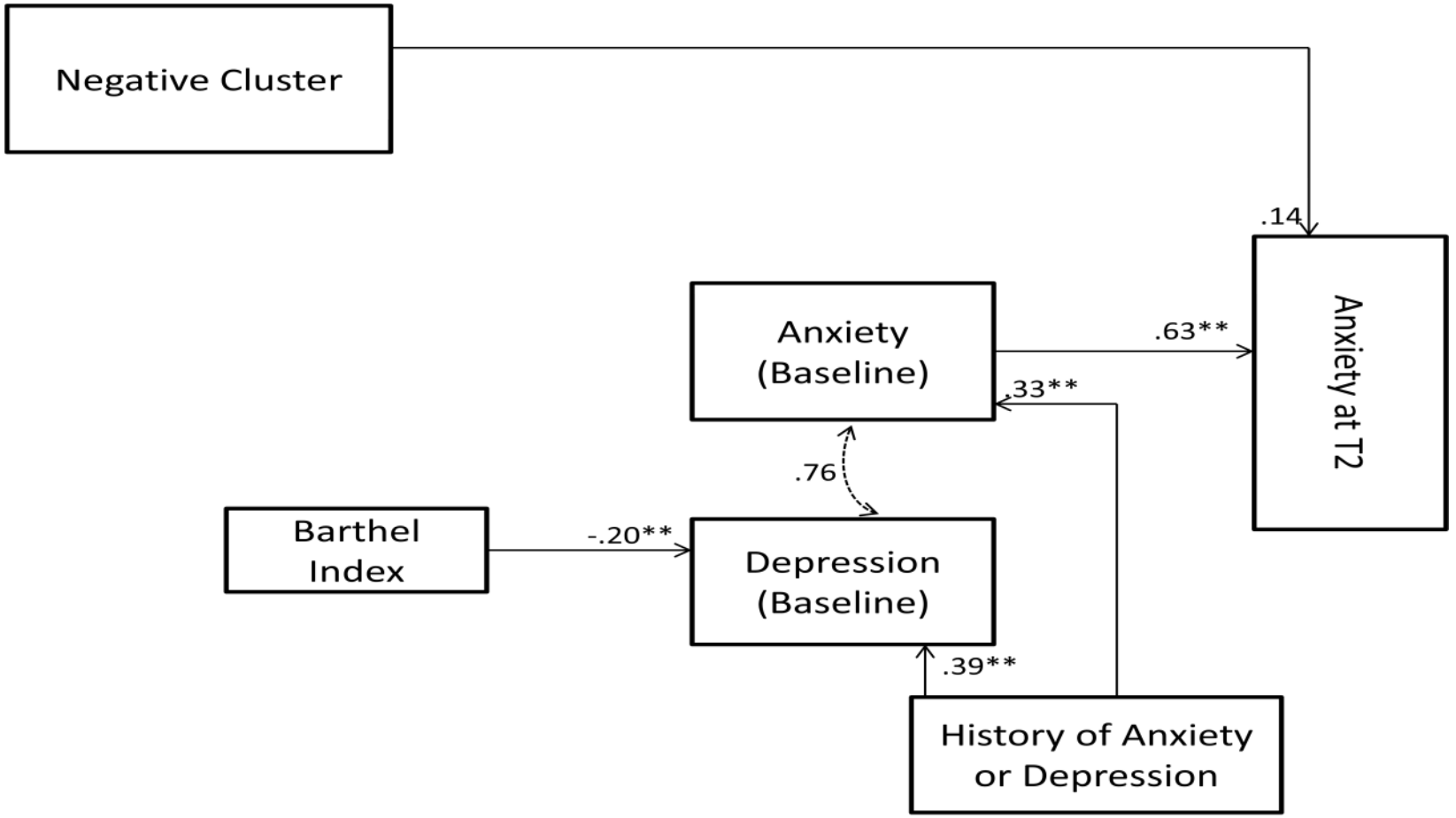


Figure 8-6 SEM Trimmed Model

*p<.05, **P<.01

8.6 Summary of longitudinal analysis

- Individuals lost to follow-up had higher levels of baseline depression and increased impairment on activities of daily living compared to those who returned their follow-up questionnaire, however they did not differ in their illness representations
- There was a non statistically significant increase in the level of anxiety symptoms, while the level of depression remained constant over time. Over half of individuals with anxiety at baseline remained anxious at follow-up. Additionally 16% of individuals not anxious at baseline became so at follow-up
- Overall stroke participants did not change their illness representations over time, however participants became more negative in their perceptions about the ability of treatment or personal actions to control their stroke symptoms
- Two distinct clusters of illness representations were observed, those in cluster one held more negative beliefs about their stroke, will those in cluster two had more positive beliefs
- Linear regression analysis showed that anxiety at baseline was the only significant predictor of anxiety at follow-up, these findings were supported by a structural equation model.

9 Chapter Nine: Discussion

9.1 Introduction

This chapter discusses the findings from the empirical study, and looks to contextualise this work within the larger context of research into illness representation. Limitations of the methodology are examined, and implications for clinical practice and future research explored. Concluding remarks bringing the findings from all three studies together is included.

9.2 Overview of findings

This is the first known study that has examined illness representations using the IPQ-R and explored its association with anxiety in stroke survivors. It assessed the prevalence of anxiety, and the illness representations held in a sample of community stroke survivors residing in the UK. The results of this study found that 30% of the study sample experienced significant levels of anxiety symptoms within the first six months after stroke. This is slightly higher than the overall pooled estimate of anxiety symptoms reported in the systematic review of anxiety prevalence after stroke (Campbell Burton *et al.* 2012). There are several reasons why this may have been the case. To start, the studies included in the meta-analysis were carried out in a variety of settings, in patient groups with differing levels of healthcare and used various tools and methods to assess the presence of anxiety. The aim of the prevalence review was to quantify the extent to which anxiety after stroke occurs. Any attempt to make a direct comparison regarding the frequency of anxiety observed in this study with the findings from the prevalence review would be difficult. Comparison with individual studies may be more insightful. For example, a community based UK study that assessed anxiety one month post-stroke in a sample of 84 stroke survivors and used the same HADS-A threshold to define anxiety as the empirical study in this thesis, found the prevalence of anxiety to be 26% (95%CI 17%-36%) (Lincoln *et al.* 1998). Another study conducted in four stroke rehabilitation centres in Europe found that individuals from the UK site had anxiety prevalence rates of 30%-37% two to four months post stroke (De Wit *et al.* 2008). While those findings are not directly comparable with this study because of the

different patient populations and HADS-A cut-off score used to define anxiety, the authors note that rehabilitation programs have been found to be less intensive in the UK compared to some other European countries which has resulted in less favourable motor and functional recovery. Such factors are also likely to be associated with levels of anxiety. The higher prevalence could also be attributed to a possible cohort effect discussed in section 2.9, whereby anxiety prevalence has been found to increase across generations. Causes for this generational shift are unclear but changes in social trends such as increasing divorce rates and a perception of decreased social cohesion have been cited as possible reasons (Twenge 2000). Studies included in the meta-analysis on the prevalence of anxiety post-stroke, carried out assessments in stroke survivors as far back as 1981. Current stroke survivors have likely experienced different social circumstances which may have contributed to the higher prevalence of anxiety that was observed in this sample relative to those in the past.

Another explanation for the higher prevalence could be the inclusion of individuals with TIA, who comprised 40% of the study sample. Worry about having a "full" stroke in the future may have led to higher levels of anxiety. Stratifying studies in the anxiety after stroke prevalence systematic review on the basis of whether or not they included patients with TIA was not part of the planned analyses, hence further studies would need to be carried out to validate this hypothesis.

Another finding of interest is that the majority of individuals with anxiety (58%) did not have co-morbid depression. By follow-up two thirds of individuals who had co-morbid depression at baseline indicated they were no longer experiencing mental health distress at follow-up, however only a third of individuals with anxiety only at baseline indicated respite of their anxiety symptoms at follow-up. A possible explanation for this finding is that depression may garner more clinical attention and attempts may have been made to treat it. In so doing the anxiety that was also present may have been addressed unintentionally. In terms of chronology of mental health distress, a third of individuals who only had anxiety at baseline were found to have co-morbid depression at follow-up, and provides some support for the hypothesis that anxiety often precedes depression (Michael, Zetsche and Margraf 2007). However this finding should be interpreted with caution, as cell sizes were very small and estimates may not be stable.

Unadjusted univariate analysis found that impairment in activities of daily living was the only factor that was significantly different between individuals defined as anxious compared to those who were not anxious. Recovering to pre-stroke levels of functioning is likely a goal for many patients, and if they are unable to attain these goals this could lead to experiencing increased levels of anxiety. Although not statistically significant, a larger proportion of individuals under 65 years of age or those with a history of anxiety or depression, were found to have anxiety at baseline. No other variables (gender, living status, type of stroke, number of co-morbidities, score on cognitive screening test administered at recruitment) investigated in the univariate analysis was associated with anxiety. These results appear to follow the trends identified in the studies collated in the correlates section of the prevalence systematic review whereby no consistent association was observed between gender and anxiety, and only 25% of studies found an association between anxiety and age. There was an even split amongst studies examining the relationship between impairment in activities of daily living and anxiety, whereby half the studies reported an inverse correlation, and the other of half reported no association.

Few studies have used the IPQ-R previously, so it was important to assess the internal reliability of the scale. Overall the reliability of the individual domains in the scale was found to be good. With the exception of the personal control domain, all of the IPQ-R subscales had values above 0.80. The personal control domain was found to be 0.72, which is still considered acceptable. A similar finding was also observed in two other small stroke studies (Ford 2007; Twiddy 2008). Lower internal reliability on the personal control domain could imply that stroke survivors do not view personal control as a singular construct or are unclear about the role they may play in managing symptoms associated with stroke. Another possibility is that quantitative questionnaires may not be an adequate method from which to assess beliefs about illness. The original work by Leventhal and colleagues sought to elicit individual illness representations by conducting in-depth qualitative interviews, and adopted a quantitative approach mainly for the purpose of having the ability to generalise findings. The lower level of internal reliability could also be due to the study samples that were investigated. All three of these studies used clinical samples or had significant non-response from the eligible population and may not necessarily reflect the stroke population in general.

Overall, participants reported an average of six illness identity symptoms they felt were attributed to their stroke. Fatigue was the most commonly reported symptom, however weakness, tingling or numbness in extremities, loss of strength, forgetfulness and dizziness were also frequently endorsed as being attributed to stroke. The impact that these symptoms could have on the post-stroke experience is immense. For example, post stroke fatigue has been found to interfere with the rehabilitation process and may increase the risk of depression (Morley, Jackson and Mead 2005; Hackett and Anderson 2005). Dizziness is associated with an increased risk of falling. A case-control study that matched 60 older adults with chronic dizziness with healthy controls found that nearly half in the dizzy group reported a fear of falling, while only 3% of the healthy controls expressed a similar fear (Burker *et al.* 1995). Additionally, symptoms such as unilateral weakness and sensory symptoms have been found to be the most commonly reported symptoms during a stroke (Hankey 2002). Fear of stroke re-occurrence is also common. It is possible that individuals who experience the illness identity symptoms will seek to give them some sort of meaning. That they are not actually having another stroke, yet still experiencing the ambiguous symptoms that are associated with the stroke event, could contribute to an increased level of anxiety.

In terms of the other domains of illness representations held, beliefs about personal control and treatment control were strong. Finding relevant comparative data for this study was challenging because much of the existing literature is based on the original version of the IPQ, employed a different method of scoring than prescribed by the IPQ-R authors, or was not available for detailed examination (Aalto *et al.* 2005; Kaptein *et al.* 2006; Evans and Norman 2009; MacLeod, Abdullah and Wilkinson 2010). However, one large scale Canadian study assessed illness representations in cardiovascular patients with myocardial infarction, unstable angina, congestive heart failure, percutaneous coronary intervention (PCI), or coronary artery bypass graft surgery (CABG) and their association with depression (Grace *et al.* 2005). Relative to this group, stroke patients in this study thought the symptoms of their stroke would be significantly less chronic in nature, and have less of a consequence on their life. This could be due to the fact that 40% of the individuals in this study sample had a TIA, and they may have interpreted their health threat as something that would resolve relatively quickly. There is still a prevailing belief that TIAs are less serious than stroke, and

patients are sometimes told they have only had a ‘mini-stroke’ or ‘not a full stroke’. On the other hand, although a significant proportion of participants in this study held strong views about personal control and treatment control, those in the cardiovascular group had significantly stronger beliefs in this regard. Perhaps this is a function of there being a more established framework for secondary prevention measures for heart disease whereby patients are encouraged to make lifestyle modifications or take certain drugs to reduce their risk of recurrence, although similar advice is provided to stroke survivors as well.

In terms of causal beliefs about stroke, age was the factor most frequently identified by participants as a possible cause of stroke. However only 50% of the study sample said that they believed this to be the case. Other factors, such as diet, smoking and alcohol consumption, were identified less often as possible causes of stroke. That these factors were not more readily recognised as risk factors for stroke highlights the need for health education. Stroke survivors are provided with information packs about their stroke which include a wealth of information, however there may be some incongruence between information that is provided, and what is being understood by stroke survivors. Additionally, overwork and personal behaviour were endorsed by roughly 25% as causal factors of stroke. Previous studies have noted that a feeling of fear associated with the possibility of having another stroke will drive a search for a cause and if the perceived cause is associated with bad life habits, it could support the use of active compensation strategies, such as adopting health behaviours (Rochette *et al.* 2006). In this regards an awareness of illness beliefs could further support the development of targeted individualised information about stroke to empower survivors with knowledge about modifiable factors they could use to help prevent another stroke or improve their overall health.

On a whole, the patterns of relationships among illness perceptions showed logical trends similar to those observed in a meta-analysis of 45 studies in which illness representation domain inter-correlations were examined (Hagger and Orbell 2003). Illness identity was significantly and positively associated with chronic timeline, cyclical timeline, and consequences. However, no significant negative correlations between illness identity and the control domains, or consequence and control domains were observed in this study. Emotional representations were significantly and positively associated with identity, timeline (chronic and cyclical), and consequence domains, and negatively associated with

coherence. A similar pattern of inter-correlations has been reported in a small study of stroke patients (Ford 2007). This study also found significant associations between individuals who attributed a higher symptom burden to their stroke with the tendency to believe that the stroke symptoms would have a longer duration and more serious consequences on their lives. The study also found that coherence only had significant associations with personal control and emotional representations. Individuals had a significant positive correlation with personal control beliefs and a significant negative correlation with emotional representations. However inter-correlations observed in the validation study of the IPQ-R showed significant negative correlations between emotional representations and personal and treatment control domains, which were not found in this study. This may simply have occurred because the patient population used to validate the IPQ-R was likely had a different illness experience. The validation sample included individuals with diabetes, asthma, chronic pain and rheumatoid arthritis. However they did include cardiovascular patients, but stratified inter-correlations were not provided for this sub-group of patients.

9.2.1 Are there differences in illness representations between anxious and non-anxious stroke survivors

The multivariate analysis of variance showed that those with anxiety had higher illness identity symptom burden, felt that their stroke symptoms were less predictable, would have greater consequences, and had a greater emotional representations relative to those without any mental health distress. This study also provided the opportunity to assess whether there would be differential patterns of illness representations between individuals with anxiety and depression. No difference in illness representations were observed, except that those defined as depressed had an even higher illness identity burden than those defined as anxious. The finding of there being no significant difference in illness representations between the anxious and depressed individuals has not been examined in other stroke patient groups. However, a cross-sectional study in 108 patients with tuberculosis whereby 46% had depression and 47% had anxiety, as defined by a score of greater than 11 on the HADS-A and HADS-D sub-scales, found that the correlation between the individual IPQ-R domains were the same for both those defined as depressed and those with anxiety (Husain *et al.* 2008). This finding could be interpreted in several ways. It has

been suggested that anxiety may be a precursor to depression, such that those defined as anxious, will ultimately become depressed and it is just that they have been picked up at an earlier stage in their mental health trajectory. The data in this study suggest that this is possible, as a significant positive correlation was observed between time post-stroke and depression but not anxiety. Another possibility that could be considered is to interpret the findings through the tri-partite theory of anxiety and depression. The tri-partite theory purports that both share a common component of negative affect and are differentiated only by the low positive affect in those with depression, while those with anxiety have high physiological arousal (Clark and Watson 1991). Due to the way the data were stratified, 71% of those defined as depressed for the purpose of the analysis also had anxiety. The higher symptom burden noted by these "depressed" individuals could represent the added attention to physical symptoms that would occur in individuals who are anxious.

9.2.2 Are illness representations associated with anxiety at baseline

The full regression model showed that after controlling for clinical and demographic variables, illness identity and emotional representations were the only factors that were significant predictors of anxiety. Overall the full model explained 49% of the variance in anxiety scores. Illness identity accounted for 20% of the variance, and emotional representations contributed 13%. One cross-sectional study of 168 individuals with multiple sclerosis that conducted a multiple regression analysis, found that illness identity was a significant predictor of anxiety, as identified on the HADS-A subscale (Jopson and Moss-Morris 2003). However they also found that increasing symptom cyclicality and having a greater understanding of their condition, were also predictive of anxiety. While that study provides useful comparative information with another neurological condition, it suffers from several methodological limitations which may limit the validity of the findings as it was only able to recruit 40% of the eligible patient population. Non-responders may have had significantly different illness beliefs and levels of anxiety than those who participated. Furthermore, as this was a cross-sectional study, the direction of the relationships between the illness representation domains and anxiety cannot be established (Jopson and Moss-Morris 2003). The study in multiple sclerosis patients also adjusted for different variables than the empirical study in this thesis and did not take into account the role of emotional representations.

Another aspect that needs to be taken into consideration is that emotional representations have been found to have a weak to moderate correlation with affective dispositions (Moss-Morris *et al.* 2002). In this study a strong correlation was observed between anxiety and emotional representations (r_s= 0.62), hence the regression model that includes this domain of the CSM could be measuring a personality trait tendency, such as having high tendency of anxiety or depression. High trait anxiety has been found to moderate levels of state anxiety which arise as a result of situational events (Eysenck and Eysenck 1980; Spindler *et al.* 2009; Tang and Gibson 2005). However, the questions used to assess emotional representations of a health threat were not designed to measure trait disposition, so such an assertion cannot be made with any certainty.

9.2.3 Does the prevalence of anxiety and anxiety symptom severity change over time

In this study, 9 (56%) individuals who were anxious at baseline remained anxious at follow-up. Anxiety symptom severity was higher in this group of participants who were anxious throughout, and there was a non statistically significant increase in their level of anxiety during the study period. Additionally, 16% of individuals without anxiety at baseline were found to be anxious at follow-up. Only one other study has used the HADS-A to evaluate the time-course of anxiety after stroke (De Wit *et al.* 2008). This study assessed the prevalence of anxiety two, four and six months post-stroke in a group of 505 patients admitted to rehabilitation centres in four European countries. It found that the severity of anxiety symptoms decreased significantly between four and six months post-stroke, from a median score of 5 to a median score of 4. The study also found that 41 (40%) stroke survivors with anxiety at two months post-stroke remained anxious throughout the four month observation period (De Wit *et al.* 2008). Additionally, 20% were anxious at two and four months but not at six months post-stroke, and one third were only anxious at the two month mark post-stroke. Furthermore 37 (11%) individuals who initially were not anxious at baseline became so at four months post-stroke, and 54% of them remained anxious at six months post-stroke. At six months post-stroke 22 (7%) individuals became anxious for the first time. It is not possible to make a direct comparison between this study and Dewit et al. 2008 because they used a cut-off score of greater than or equal to eight on the HADS-A subscale to define anxiety, their study population was substantially different and

assessments were made at different times post stroke. However in all the findings support the notion that anxiety tends to be chronic and the pattern of prevalence can be complex even over a short period of time. Whilst this study only had one follow-up period after baseline assessment, it is possible that a similar trend may have been observed.

9.2.4 Do stroke survivors change their illness representations over time

Overall as a group, the illness representations of the study participants remained relatively stable over time. Significant changes were only observed in perceptions about treatment control and personal control, both of which became significantly more negative over time. These results replicate findings observed in a small study of stroke patients and carers (Twiddy 2008). That study used the IPQ-R to assess illness representations in a group of 42 patient-carer dyads at three and six months post stroke and found that views about personal control and treatment control became significantly more negative over time. However, nearly a quarter of respondents in that study were unavailable for follow-up assessment so the reliability of the findings are questionable. Views about controllability have not been explored in the stroke literature, but perhaps it reflects frustration due to the plateau in recovery that many stroke survivors experience three to six months post-stroke, which could lead to feeling there is nothing that will improve their stroke associated symptoms (Vanhook 2009).

That none of the other domains of illness perceptions changed over time, is in contrast to what was proposed by Leventhal and colleagues in their seminal investigations into illness representations (Leventhal, Meyer and Nerenz 1980). However, findings from this study are congruent with other observational longitudinal studies that have found that not all domains of illness representations are updated over time. A six year longitudinal study of 241 osteoarthritis patients found that there were no changes in the identity, consequence and treatment control domains in the study population as a whole over time (Kaptein *et al.* 2010). A smaller study in a group of 87 cardiovascular patients found that overall, only the cyclicality and personal control domains changed between baseline and three month follow-up (Fischer *et al.* 2010). However additional analysis in the cardiovascular patients revealed that those who held more positive views about the goals they had achieved from treatment had significantly different patterns of change in their

illness representations relative to those who held more negative opinions about the goals they had achieved through treatment (Fischer *et al.* 2010). This is inline with other assumptions of the CSM whereby it has been proposed that an individuals appraisal of events can influence whether or not there are changes in illness representations (Leventhal, Nerenz and Steel 1984).

Another possible explanation for the lack of change in illness representations could be the methods used to examine changes in beliefs. Simple change scores only measures overall group differences, however this method may mask individual level differences. Cluster analysis, which took into account the overall illness schema of individuals uncovered two groups of participants. One group held more negative views about their stroke, while the other group was defined as being more positive. When the overall illness schema was taken into account, with the exception of coherence and emotional perceptions, significant changes on all of the other domains were observed. Those in the "positive" cluster group reported a significant decrease in symptoms attributed to stroke, chronicity of their condition, symptom unpredictability, and consequence to life. Conversely, this group reported a significant increase in beliefs about personal actions and treatment to cure stroke symptoms. Interestingly those in the positive cluster reported an increase in emotional representations, meaning that with the passage of time the stroke was likely to make them feel more upset, depressed, or afraid, yet they showed a non statistically significant decline in their level of anxiety from baseline. The emotional representation of the stroke for those in the negative cluster decreased, hence these individuals became less angry, depressed or afraid over time. This finding is contrary to what has been observed in studies that have used cluster analysis to examine changes in illness representations over time (Kaptein *et al.* 2010). Although the difference in emotional representations between the positive and negative cluster in this study was not significant, it is unclear whether this trend is a genuine paradoxical consequence of becoming more positive in beliefs about stroke or simply a phenomenon unique to this study sample. Another interpretation could be that becoming more emotional is associated with a coping strategy whereby actively expressing negative emotions towards the stroke is in some ways helpful.

9.2.5 Do illness representations predict anxiety at follow-up

The longitudinal study design allowed for examination into factors that were predictive of anxiety at follow-up. After adjusting for baseline anxiety, none of the other variables entered into the model, including illness representation cluster, were significant predictors of anxiety at follow-up. No other study has used the common-sense model of illness representations to predict anxiety longitudinally. One study that assessed beliefs about locus of control to predict anxiety three years post-stroke found that none of the other predictor variables (disability in activities of daily living at admission, exercise frequency, satisfaction with treatment or health beliefs) were significant predictors of anxiety at follow-up after adjusting for anxiety levels at baseline (Morrison *et al.* 2005). A similar finding was observed in a study of Parkinson's patients whereby baseline anxiety was found to be the most significant predictor of anxiety at six month follow-up. However in this case, the personal control domain of the CSM also explained a significant proportion of the variance in anxiety at follow-up (Evans and Norman 2009). Another study that looked at illness representations in a sample of patients with angina also found that baseline anxiety was the only significant predictor of anxiety two years after the onset of coronary heart disease (Furze *et al.* 2005). These findings need to be interpreted with caution. To start there is a paucity of longitudinal investigations into illness beliefs and anxiety, so it is possible if more studies were available that different trends would be observed. Also, these studies suffered from several limitations including small sample size, a high proportion of individuals lost to follow-up and strict restrictions on individuals' participating in the study. Additionally they did not always include all domains of illness representations in the regression model.

A structural equation model (SEM) to predict anxiety at follow-up supported findings from the regression analysis, in that it also found that baseline anxiety was the only significant predictor of anxiety at follow-up. The SEM also allowed for examination of associations between the independent variables. There was no significant association between age and illness cluster or gender and illness cluster. Additionally, impairment in activities of daily living was not significantly associated with having a negative belief. This model needs to be interpreted with caution. To start the sample size at follow-up was smaller than baseline and as such the parameter estimates may be unstable, as the ratio of

participants to variable was less than the minimum 5:1 which has been suggested (Fabrigar, Porter and Norris 2010). Others have suggested a minimum sample as high as 200 is needed, however this view has been criticised as being overly simplistic as SEM models have been found to perform well in samples as small as 50 to 100 (Iacobucci 2010). The consequence of smaller sample size may be less than ideal values on the fit indices, which was not observed in this study. Additionally, not all relationships could be examined given the sample size. As with any SEM, an alternate pattern of fit is plausible, hence all these findings suggest is that the model proposed cannot be rejected, however an improved but untested model could exist. Ideally, these findings would need to be replicated in a larger sample of stroke, before drawing conclusions.

9.3 Consideration of methodology

A major strength of this study is that it used a longitudinal follow-up approach to assess change in the level of anxiety symptoms and illness representations over time. It also used the HADS-A cut-off score of ≥11 which meant that the individuals defined as anxious were more likely to be experiencing clinically significant levels of distress. There were however several limitations in the methodology that may have had an impact on the findings. To start, the inclusion criteria excluded individuals lacking proficiency in the English language, global aphasia, or had significant terminal illnesses. Ideally, all first-time stroke patients should be approached for inclusion into a study. A researcher could have assisted in obtaining responses from individuals who would struggle with the take home questionnaire. Unfortunately, this was not possible in the outpatient clinic setting where recruitment occurred and there were insufficient resources to support endeavours such as a researcher travelling to the participants home to administer the questionnaire. The inclusion criteria in this study is similar to many of those used in the published literature (see Table 4-2) and is a limitation of much of the research carried out into the non-acute phase in stroke survivors.

The timeframe post stroke for recruitment into the study was broad (i.e. 0-6 months post stroke), as such there was likely substantial heterogeneity amongst participants in their stage of recovery, which in itself may have attenuated any associations examined. Those that responded at baseline were on average two months post-stroke, while those who did

not were close to three months post-stroke. This suggests there may be difficulty in carrying out research into longer term outcomes post-stroke. Individuals may be eager to participate in research immediately after stroke but due to the challenges of managing life after stroke may become less willing to do so with the passage of time. Given the many challenges of life post-stroke, study participants who were lost at follow-up may have been experiencing higher levels of mental health distress that prevented continuation in the study and reduced the validity of findings. At baseline, individuals who were lost to follow-up had similar levels of anxiety as those who responded at follow-up, however those lost to follow-up were found to have reported higher levels of depression at baseline. The reduced sample size at time two meant there was a loss of statistical power to detect a difference between those in the positive and negative illness belief cluster, and may explain why illness beliefs did not predict anxiety at follow-up.

Another factor to consider is that overall findings may be less applicable to younger stroke survivors (i.e. those under 65 years of age) as response rates were significantly lower in this group relative to those over 65 years of age. Whether lack of participation of younger stroke patients is a widespread issue or unique to this study is unclear. In this study the mean age of study participants was 70 years, which is similar to the mean age observed in the studies included in the systematic review of prevalence of anxiety post-stroke. That approximately 40% of the eligible stroke participants were not recruited into the study for various reasons including failing to present for clinic appointment, not being referred by clinic staff or refusing to participate also calls into question the generalisability of the study findings. Individuals who were not recruited may have varied significantly in their level of anxiety or in their illness beliefs. However four of five community based studies that examined anxiety after stroke had similar participation consent rates that ranged from 52% and 61% (Ahlsio *et al.* 1984; Bruggimann *et al.* 2006; Gillespie 1997; Visser-Keizer *et al.* 2002) with only one study able to recruit more than 80% of the eligible stroke population (Lincoln *et al.* 1998). Future community based stroke studies should consider pilot testing the recruitment process to identify problematic issues that may arise before commencing the actual study. Another strategy could be to request permission to contact patients who were missed in clinic, however this would require further ethical approvals. Additionally, recruitment only occurred at one site in Sheffield. Individuals attending other stroke clinics

in the city could not be contacted. While there is no obvious reason to think stroke survivors attending other clinics differed significantly from those attending the site where recruitment occurred, the possibility exists that they may have. However the location of stroke outpatient clinic attendance is based on patient choice and convenience and perhaps more complicated cases being seen at the teaching hospital, which is where recruitment occurred.

The MANOVA and discriminant analysis carried out to disentangle the differences in illness representation between those with anxiety and those with depression post stroke was less than adequate. Ideally, the study sample should have been separated into four groups as opposed to three (no mental health distress, anxiety only, depression only, and co-morbid anxiety and depression). This would have been the best method of quantifying the additional impact of depression on anxiety however the sample size was too small to conduct such an analysis. Hence it is likely that the lack of difference observed could be due to a lack of statistical power to detect a difference, especially given the significant number of individuals defined as depressed who also had anxiety.

Information about stroke hemisphere lesion location and the Oxford Stroke Classification was unavailable in the outpatient clinic files of more than half of the participants (this information would have been recorded elsewhere). Hence no association between stroke lesion location and anxiety could be examined. Additionally, the study sample was heterogeneous in that it included individuals with who had a full stroke and those with a TIA. It is possible that residual deficits and the stroke experience could have differed between these two groups of stroke survivors. This study was not powered in such a way as to test for possible differences between those with stroke and those with TIA and conducting multiple post-hoc analyses would lead to increased likelihood of type one error. On the other hand, the inclusion of individuals with TIA means that anxiety and illness representations was obtained from a broader spectrum of stroke survivors.

Due to the sample size, another limitation of this study was that causal beliefs about stroke were not included in the overall model, hence any impact they may have in predicting anxiety could not be examined. Scale authors recommend conducting a factor analysis of causal beliefs, to identify broad categories rather than including only individual

questions about causal beliefs into a regression model. It is not unusual to see regression models that have not included all CSM domains for a variety of reasons that include limitations in sample size, or research interest, and this limitation has occurred in other studies that have assessed associations between the CSM and outcomes in stroke patients (Ford 2007). Furthermore, the section in the survey that asked about causal beliefs about stroke was poorly completed, with some questions having high item non-response. Only participants who responded to the respective causal question were included in the results. Item non-response may have changed the pattern of causal attributions of stroke that were observed. Questions about causal beliefs were at the end of the three part section on illness representations, and perhaps participants were experiencing questionnaire fatigue at this stage. The only stroke study to provide information on causal beliefs in stroke survivors had the IPQ-R administered by a researcher hence their may have been time to take breaks throughout survey, yet ensure that all questions were complete (Twiddy, House and Jones, 2012).

This study asked about anxiety and depression symptoms in the past week. There is always some uncertainty regarding the extent to which information obtained from a questionnaire reflect 'usual' levels of mental health distress. The responses provided could be influenced by a variety of external circumstances, such as the recent loss of a loved one. A diagnostic interview by a trained psychiatry or psychology professional is the gold standard for determining the presence of anxiety. Additionally, one third of the respondents indicated they required help in completing the questionnaire. Having someone read the questions was cited as the most common source of aid required. Ideally, it would be best for an individual to complete the questionnaire on their own without any assistance from others. The extent to which stroke survivors who needed help may have provided biased responses (e.g. a socially desirable answer such as saying they were not experiencing anxiety symptoms when they were) because they were in the presence of another party while completing the questionnaire is unknown. Individuals who were not forthcoming in all their responses may have impacted the validity of the findings.

Participants were not asked about coping strategies. This was intentional so as to decrease respondent burden. However coping is a central component of the current Common-Sense Model. Any meditational influence of coping on the relationship between

illness representations and anxiety is unknown. However, there is substantial research that has shown a direct link between illness representations and outcome, which calls into question the proposed mediational influence of coping and outcome (Hagger and Orbell 2003). Future studies may want to consider using the short version of the illness representation questionnaire (Broadbent *et al.* 2006) given the high proportion of participants who indicated they required some sort of help in filling out the questionnaire. This could have contributed to the poor item completion in the section about causal beliefs about stroke, which meant that an in-depth investigation into this aspect of the CSM could not be carried out. Using a shorter version of the illness representation questionnaire would lessen the participant burden and provide additional time for investigation into other factors associated with anxiety after stroke.

Another limitation of this study is that the views of carers were not sought. Other research has found that the illness representations held by carers can influence the beliefs of stroke survivors (Twiddy, House and Jones 2012). Additionally, mental health distress experienced by carers could influence mental health distress experienced by the stroke survivor.

While the aim of this study was to evaluate the ability of illness representations to predict anxiety, the presence of anxiety can influence illness representations in several ways (Cameron 2003). Changes in perceptual processes due to the presence of anxiety can enhance the detection of attention to illness related symptoms (identity). Additionally it has been proposed that mood states can facilitate the retrieval of emotional memories, and anxiety can increase the prominence of the emotional and threatening content of illness representations (Forgas 2000). None of these relationships were examined in this study.

9.4 Implications for clinical practice

With the exception of illness identity, cognitive representations were found to contribute little in the way of explaining anxiety symptoms experienced by stroke survivors in this study. However, given the methodological challenges outlined in section 9.3, it is too early to dismiss the notion of illness representations being associated with anxiety after stroke. Illness beliefs may also influence other post-stroke outcomes that were not evaluated in this study, such as engagement with rehabilitation or re-integration into life

post-stroke. Also of interest was the large proportion of individuals who had anxiety that was not co-morbid with depression. This should serve as a reminder that anxious distress is common and protocols need to be established that adequately address their needs.

When an individual is diagnosed with a health condition, a pattern of illness representations will develop. These representations may serve as key determinants of behaviour directed at managing the illness, or may be directly associated with outcomes arising as a result of the illness, such as anxiety (Petrie and Weinman 2006). Knowledge of these representations are clinically relevant because they may help to uncover and understand patient aspirations and expectations throughout the rehabilitation process and beyond. Furthermore, patient adjustment and recovery have been found to improve when illness representations were modified from a more negative stance to a more positive stance (Petrie *et al.* 2002). Despite this, patients are rarely asked about their views of their illness (Petrie and Weinman 2006). It is possible that for some stroke survivors, a chance to share their beliefs about their condition could be seen as empowering and as an opportunity for them to engage with and influence their rehabilitation process.

Information about illness representations can be obtained informally by way of asking open ended questions, or through the use of formal assessment tools. The IPQ-R is likely too lengthy for use in clinical settings such as outpatient clinics of GP clinics. Alternatively, the brief nine item version of the IPQ-R (Broadbent *et al.* 2006) could be useful for providing a snapshot of patient views of their illness and would likely be more appropriate for use in the fast-pace settings of outpatient clinics. However validation studies of the brief version of the IPQ-R in stroke survivors would need to be conducted beforehand. Furthermore, unlike scales such as the HADS that provide some guidance around cut-off score thresholds, normative data for the IPQ-R has yet to be established. Tracking of illness representations would need to take a relativist approach, in that comparisons would need to be made over time to determine whether the views of stroke survivors were becoming more positive or more negative. This raises another issue in that once a screen has taken place, something may need to be done. If the appropriate resources are not in place, this calls into question the aim of screening in the first place. Screening for anxiety has already proved challenging with a lack of access to trained psychological resources and costs associated with re-organising the workflow cited as a major limitations (Morris *et al.* 2012). It is likely that

similar challenges would exist if screening for illness representations after stroke were recommended to become part of routine practice. However, there is potential to learn from some of the national Stroke Improvement Programme case studies that have focused on improving psychological services for stroke survivors. For example two individualised mood and cognition screening projects carried out by the Bassetlaw Community Health Consortium, the Nottinghampshire Healthcare NHS Trust, and the Sherwood Forest Hospitals NHS Foundatation Trust in acute and community settings found that initiatives were more successful when they were embedded into routine practice, staff understood the reasons for screening and there was some flexibility in the measures that were administered (Stroke Improvement programme 2011a).

9.5 Research gaps and implications for future work

In terms of future research regarding illness representations, stroke and anxiety, various other possible relationships were not examined but could prove to be of interest and have some clinical utility. For example, factors and sources of information that contribute to the development of illness representations were not examined. Having an understanding of how representations develop is as important as knowing what the representations are. Investigation into the health economic cost of anxiety after stroke also needs to be conducted. For example, there is limited information the association between anxiety after stroke and other outcomes such as quality of life, social reintegration, returning to work and health service utilisation.

This study used a quantitative survey approach to elicit information about illness representations in stroke survivors. However the original ethos of the common-sense model was for participants to be able to use their own words and language to characterise a threat. Hence a qualitative exploration into illness representations held by stroke survivors is needed to corroborate information obtained from the IPQ-R, as the language used by stroke survivors to describe their representations may differ from that of the questionnaire.

Strategies to increase the participation of younger stroke survivors in research are required. Their experience may be substantively different from older stroke survivors, however their low participation rate meant that phenomena unique to this group could not be examined. Strategies to ensure participation amongst individuals from ethnic minority

backgrounds are also needed as none were included in this study. This was unusual given that some of the recruitment occurred in Sheffield which is an ethnically diverse city. Future studies may need to adopt a stratified sampling approach whereby the proportion of individuals recruited into the study is reflective of the population under investigation.

This study highlighted several other challenges that should be taken into consideration when conducting observational studies in stroke. To start there was competition from other local stroke studies in progress which may have increased the difficulty in obtaining the necessary research governance approvals. Much of the incentives hospitals receive for participating in research are obtained by allocating staff resources to facilitate recruitment into randomised control trials. Observational studies, and PhD studies in particular, may have limited or no funding to offset the costs incurred by hospitals and clinics for allocating staff resources for research as opposed to clinical care. Lack of such supports for lone-researchers (as is the case for many PhD projects) increases the difficulty of recruiting adequate numbers of patients into studies. As outlined in the workplan, the length of time for recruitment had to be extended by over two months. One strategy that could be utilised in the UK would be to ensure that the research study is adopted into the National Institute of Health Research portfolio system. Adoption into the portfolio system enhances the profile of a study, and it also compensates hospitals for the use of staff resources, which means that some clinical support can be provided to the researcher to assist with recruitment and data collection. If this is not possible, the feasibility of conducting this type of work within the NHS should be seriously considered. If longer term outcomes are of interest it may be advisable to seek to obtain a study sample from other sources such as stroke clubs, or by using GP patient lists. However individuals attending stroke clubs may not be representative of the larger stroke population, and depending on the study inclusion criteria, a very large number of GP clinics would need to be contacted as on average each GP sees about five new cases of stroke per year (Lee, Shafe and Cowie 2011).

High quality clinical trials, particularly of psychological interventions used to treat anxiety after stroke are needed. The Cochrane review found limited evidence of effectiveness in treating anxiety based on two small drug trials. However the inclusion criteria for these trials required participants to have co-morbid depression and limitations in their design, such as a lack of a placebo control arm in both studies, introduced

methodological bias into the results. Future intervention studies will need to include stroke survivors with anxiety only. Another limitation of both the empirical study and the systematic review of the prevalence of anxiety after stroke that will need to be addressed in future work is that it is uncertain if it is the stroke that has caused the anxiety. The possibility exists that the anxiety may have been present prior to the stroke. Also anxiety may serve as a risk factor for stroke. Longitudinal investigation is required to clarify this matter. Projects such as the NIHR CLAHRC funded South Yorkshire Cohort Study which is collecting longitudinal information for the next 20 years on a range of long-term conditions including stroke and anxiety may help clarify the relationship between the two. Such a large scale cohort study could also facilitate an investigation into illness representations and their association with anxiety post stroke that would provide more robust information than that obtained in the empirical study of this thesis.

9.6 Final Remarks

The high quality systematic review of observational studies established that approximately a quarter of stroke survivors experience anxiety after stroke. Currently there is insufficient evidence from randomised control trials to guide clinical practice for interventions to treat anxiety after stroke and none of the trials assessed the effectiveness of a psychological intervention. A key finding from the empirical study is that associating a higher number of symptoms to ones stroke, and having more of an emotional reaction to the stroke were significantly associated with anxiety. It also found that the majority of participants generally became more negative in their views about stroke, and in so doing showed an increasing trend in their levels of anxiety. Perhaps of greatest interest was the large proportion of individuals who were found to have anxiety that was not co-morbid with depression.

The work carried out in this thesis was novel, in that it provided a high quality estimate of the prevalence of anxiety after stroke based on a well conducted systematic review and added to the limited number of empirical studies in which longitudinal changes in illness representations were assessed. Investigation into anxiety after stroke, falls under the wider health remit to improve outcomes for individuals with mental health problems (Department

of Health 2011), and would contribute to the “no health without mental health” strategic direction of care provision and research.

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Appendix A

Systematic Review Search Strategy (adapted for different databases)
1. exp Cerebrovascular Disorders/
2. stroke*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. (poststroke* or post-stroke* or cva*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. ((cerebr* or brain* or cerebellar* or cerebellum* or vertebrobasilar*) adj2 (infarct* or ischemi* or ischaemi* or thrombo* or emboli* or apoplex*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. ((cereb* or brain* or intracereb* or intracrani* or subarachnoid) adj2 (haemorrhag* or hemorrhag* or bleed*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. 1 or 2 or 3 or 4 or 5
7. exp Adjustment Disorders/
8. exp Anxiety Disorders/
9. exp Neurotic Disorders/
10. Mental Disorders/
11. anxiet*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. distress*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. (neuros* or neurotic*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. (depersonalization or depersonalisation or derealization or derealisation).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15. fear.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16. (worry* or worri* or apprehens*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. (tension* adj2 symptom*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
18. ((avoidanc* or avoidant*) adj2 (behaviour or behavior or symptom*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
19. (autonomic adj2 (arousal* or symptom*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. (hyperventilation adj2 (symptom* or syndrom*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 6 and 21

Summary of studies excluded from the systematic review of anxiety prevalence after stroke

Study	*Description*
Ma 2005	*Design: Case-control* *Recruitment: Selected from neurology department (methods not described)* *Setting: Hospital* *Location: China* *Participants: Clinical diagnosis of stroke* *Time at assessment: 2-3 weeks post-stroke* *Diagnostic/ Screening tool: Self-Rating Anxiety Scale*
Zhang 2005	*Design: Case-control* *Recruitment: All patients admitted to ward* *Setting: Hospital* *Location: China* *Participants: 1st ever stroke diagnosed by CT or MRI* *Time at assessment: 1 month post stroke* *Diagnostic/ Screening tool: Symptom Checklist 90 (SCL-90)*
Lucev 2007	*Design: Cohort study* *Recruitment: Not described* *Setting: Community* *Location: Croatia* *Participants: Clinical diagnosis of stroke* *Time at assessment: 3 and 12 months post stroke* *Diagnostic/ Screening tool: Self rating anxiety scale*
Lee 2009	*Design: Cohort* *Recruitment: Consecutive admissions* *Setting: Community* *Location: Hong Kong* *Participants: 1st ever ischaemic stroke patients* *Time at assessment: 1 and 6 months* *Diagnostic/ Screening tool:*
Radziuviene 2009	*Design: Cohort* *Recruitment: Consecutive discharge records* *Setting: Community* *Location: Lithuania* *Participants: Stroke (not described)* *Time at assessment: 1-4 years post stroke* *Diagnostic/ Screening tool:*
Matuja 1993	*Design: Cohort* *Recruitment: Consecutive admissions* *Setting: Hospital* *Location: Tanzania* *Participants: 1st ever stroke confirmed by CT* *Time at assessment:* *Diagnostic/ Screening tool: Psychiatric interview (Present State Examination)*
Huang 2009	*Design: Case-control*

	Recruitment: In hospital recruitment *Setting: Hospital* *Location: China* *Participants: Stroke confirmed by CT or MRI* *Time at assessment: 2 weeks post stroke* *Diagnostic/ Screening tool: Hamilton Anxiety Scale*
Mcfarlane 1987	*Design: Cohort* *Recruitment: consecutive admissions* *Setting: Hospital* *Location: Australia* *Participants: Clinical diagnosis of stroke* *Time at assessment: 2 weeks, 3 & 15 months post-stroke* *Diagnostic/ Screening tool: Middlesex Hospital Questionnaire (contains anxiety subscale)*
Oladiji 2009	*Design: Cohort* *Recruitment: Not described* *Setting: Hospital* *Location: Nigeria* *Participants: WHO definition of stroke* *Time at assessment: Not provided* *Diagnostic/ Screening tool: Depression Anxiety Stress Scale*

Appendix B

Names of individuals involved in the Cochrane systematic review

- ACB- Alexia Campbell Burton
- CW- Caroline Watkins
- DG- David Gillespie
- EL- Elizabeth Lightbody
- JH- John Holmes
- JY- Jenni Murray
- PK- Peter Knapp

MEDLINE search strategy for Cochrane systematic review
1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp “intracranial embolism and thrombosis”/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$or hematoma$ or bleed$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. brain injuries/ or brain injury, chronic/
8. or/1-7
9. anxiety/
10. anxiety disorders/ or agoraphobia/ or obsessive-compulsive disorder/ or panic disorder/ or phobic disorders/ or exp stress disorders,
traumatic/
11. exp Anti-Anxiety Agents/
12. (anxiety or anxieties or anxious or agoraphobi$ or phobi$ or panic disorder$ or panic attack$ or (obsess$ adj3 compuls$) or post? traumatic stress$ or PTSD).tw.
13. (feel$ adj5 (apprehens$ or dread or disaster$ or fear$ or worry or worried or terror)).tw.
14. manifest anxiety scale/
15. or/9-14
16. 8 and 15
17. Randomized Controlled Trials as Topic/
18. random allocation/
19. Controlled Clinical Trials as Topic/
20. control groups/
21. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
22. double-blind method/
23. single-blind method/
24. Placebos/
25. placebo effect/
26. cross-over studies/
27. Multicenter Studies as Topic/
28. Therapies, Investigational/
29. Drug Evaluation/
30. Research Design/
31. Program Evaluation/
32. evaluation studies as topic/
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
36. multicenter study.pt.
37. (evaluation studies or comparative study).pt.
38. random$.tw.
39. (controlled adj5 (trial$ or stud$)).tw.

40. (clinical$ adj5 trial$).tw.
41. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
42. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
43. ((multicenter or multicentre or therapeutic) adj5 (trial$ or stud$)).tw.
44. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
45. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
46. (coin adj5 (flip or flipped or toss$)).tw.
47. (cross-over or cross over or crossover).tw.
48. placebo$.tw.
49. sham.tw.
50. (assign$ or alternate or allocat$ or counterbalance$ or multiple baseline).tw.
51. controls.tw.
52. (treatment$ adj6 order).tw.
53. or/17-52
54. 16 and 53
55. limit 54 to humans

EMBASE search strategy for Cochrane systematic review
1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke/ or stroke patient/ or stroke unit/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. paralysis/ or hemiparesis/ or hemiplegia/ or paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. brain injury/
8. or/1-7
9. anxiety/
10. exp anxiety disorder/
11. exp anxiolytic agent/
12. (anxiety or anxieties or anxious or agoraphobi$ or phobi$ or panic disorder$ or panic attack$ or (obsess$ adj3 compuls$) or post? traumatic stress$ or PTSD).tw.
13. (feel$ adj5 (apprehens$ or dread or disaster$ or fear$ or worry or worried or terror)).tw.
14. beck anxiety inventory/ or hamilton anxiety scale/ or “hospital anxiety and depression scale”/ or self-rating anxiety scale/ or state trait anxiety inventory/
15. or/9-14
16. Randomized Controlled Trial/
17. Randomization/
18. Controlled Study/
19. control group/
20. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
21. Crossover Procedure/
22. Double Blind Procedure/
23. Single Blind Procedure/ or triple blind procedure/

24. placebo/
25. Multicenter Study/
26. experimental design/ or experimental study/ or quasi experimental study/
27. experimental therapy/
28. drug comparison/ or drug dose comparison/
29. evaluation/ or “evaluation and follow-up”/ or evaluation research/ or clinical evaluation/
30. methodology/
31. “types of study”/
32. research subject/
33. Comparative Study/
34. random$.tw.
35. (controlled adj5 (trial$ or stud$)).tw.
36. (clinical$ adj5 trial$).tw.
37. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
38. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
39. ((multicenter or multicentre or therapeutic) adj5 (trial$ or stud$)).tw.
40. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
41. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
42. (coin adj5 (flip or flipped or toss$)).tw.
43. (cross-over or cross over or crossover).tw.
44. placebo$.tw.
45. sham.tw.
46. (assign$ or alternate or allocat$ or counterbalance$ or multiple baseline).tw.
47. controls.tw.
48. (treatment$ adj6 order).tw.
49. or/16-48
50. 8 and 15 and 49
51. limit 50 to human

PsycINFO search strategy for Cochrane systematic review

1. cerebrovascular disorders/ or cerebral hemorrhage/ or exp cerebral ischemia/ or cerebral small vessel disease/ or cerebrovascular accidents/ or subarachnoid hemorrhage/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$
or hematoma$ or bleed$)).tw.
5. hemiparesis/ or hemiplegia/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. brain injur$.tw.
8. or/1-7
9. exp anxiety/
10. exp anxiety disorders/ or panic/ or panic attack/ or fear/
11. anxiety management/

12. state trait anxiety inventory/ or taylor manifest anxiety scale/
13. (anxiety or anxieties or anxious or agoraphobi$ or phobi$ or panic disorder$ or panic attack$ or (obsess$ adj3 compuls$) or post? traumatic stress$ or PTSD).tw.
14. (feel$ adj5 (apprehens$ or dread or disaster$ or fear$ or worry or worried or terror)).tw.
15. or/9-14
16. 8 and 15
17. random sampling/
18. experiment controls/
19. placebo/
20. (empirical study or treatment outcome clinical trial).md.
21. clinical trials/ or Treatment Effectiveness Evaluation/
22. random$.tw.
23. (controlled adj5 (trial$ or stud$)).tw.
24. (clinical$ adj5 trial$).tw.
25. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
26. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
27. ((multicenter or multicentre or therapeutic) adj5 (trial$ or stud$)).tw.
28. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
29. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
30. (coin adj5 (flip or flipped or toss$)).tw.
31. (cross-over or cross over or crossover).tw.
32. placebo$.tw.
33. sham.tw.
34. (assign$ or alternate or allocat$ or counterbalance$ or multiple baseline).tw.
35. controls.tw.
36. (treatment$ adj6 order).tw.
37. or/17-36
38. 16 and 37

Summary table of studies excluded from the Cochrane systematic review

Study	Description
Kimura 2003	Design: Cohort Design Allocation: Unclear Blinding: Double Blind Participants: Post Stroke with clinical diagnosis of moderate to severe depression. GAD only patients excluded. This study carried out secondary analysis on a subset (27/106) participants who had co-morbid GAD. Intervention: Daily Nortriptyline 20-100 mg for 6 weeks. Dose escalated to 100 mg over duration of study; Placebo Control
Li 2005	Design: Self controlled Study Allocation: Not Applicable Blinding: Unclear Participants: Post Stroke (all had anxiety levels measured, but did not necessarily meet any criteria to be defined as anxious) Interventions: Early functional training which included component of supportive treatment without anti-anxiety or antidepressant prescriptions/ No placebo or standard care comparison
Liu 2004	Design: RCT Allocation: Number list, taking into account age, gender, and patient condition Blinding: Double Blinded Participants: Post Stroke with Anxiety (HAM-A >=14) Intervention: Group 1 received 0.2 mg alprazolam every 8 hours + fluoxetine 20mg once daily/ Group 2: alprazolam every 8 hours/ No placebo or standard care comparison
Mok 2004	Design: RCT Allocation: random drawing of lots Blinding: None, one researcher collected all data Participants: Post stroke (Anxiety assessed using Chinese State-Trait Anxiety Inventory, in all participants, but did not necessarily meet criteria to be defined as anxious) Intervention: Slow Stroke Back Massage
Morrison 1998	Design: Quasi Experimental Cohort, with Retrospective Controls Allocation: Not Applicable

	Blinding: Not Applicable Participants: Post Stroke (Level of Anxiety assessed in all participants, but not necessarily meeting criteria for anxiety) Intervention: Self-help workbook aimed at enhancing non-avoidant coping and increasing personal control over recovery
Rorsman 2006	Design: RCT Allocation: Yes; Opaque randomised envelopes, numbered consecutively produced centrally by a computer Blinding: Yes; Study Coordinator and Evaluators not granted to access on allocation Participants: Post Stroke only, (all had anxiety levels measured, but did not necessarily meet any criteria to be defined as anxious) Interventions: Group 1 Electroacupuncture, Group 2 Transcutaneous Electrical Nerve Stimulation
Wu 2008	Design: RCT Allocation: Process unclear Blinding: Not indicated Participants: Post Stroke Anxiety Neurosis (ICD-10) Interventions: Group 1 received Alprazolam, Group 2 received Accupunture/ No placebo or standard care comparison
Ye 2006	Design: RCT Allocation: Unclear (not described) Blinding: Double Blind (not described) Participants: 90 stroke survivors with co-morbid anxiety and depression defined as (>14 on HAM-A & >21 on HAM-D) Interventions: Group 1 received Paroxetine, Group 2 received Imipramine, Control group received standard care and rehabilitative training/ No placebo or standard care only comparison

Appendix C

UNIVERSITY OF LEEDS

Anxiety After Stroke

Assessment Package

Dear Participant

Thank you for taking part in my study. I have included some instructions to help you complete this package.

Step 1:
This questionnaire is divided into three sections. Please read the instructions at the beginning of each section.
If you are having difficulty completing the questionnaire, someone can help you by reading the questions and/or ticking the boxes. However please make sure the questionnaire shows your thoughts and responses.
The questionnaire should take 30 minutes to complete. If you find yourself losing interest take a break. It is important that you answer all the questions in this pack.

Step 2:
Please check through this package to make sure you have answered all the questions.

Step 3:
Return this package to me in the Freepost envelope. Do not write your name or address on the envelope.

If you have any questions or need help with this package, please telephone
Alexia Campbell Burton on 0113 343 7185

THANK-YOU

Alexia Campbell Burton/ Dr Felicity Astin
Lead Researcher/ Supervisor
School of Healthcare, University of Leeds

SECTION 1

These are some questions about how you feel. Read each statement and tick ☑ the response which comes closest to how you have been feeling in the past week. Don't take too long with your replies; your immediate reaction will probably be more accurate than a long thought out process.

1. I feel tense or wound up:

Most of the time.....	3
A lot of the time.....	2
From time to time, (occasionally).....	1
Not at all.....	0

2. I still enjoy the things I used to enjoy:

Definitely as much.....	0
Not quite so much.....	1
Only a little.....	2
Hardly at all.....	3

3. I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly.....	3
Yes, but not too badly.....	2
A little but it doesn't worry me.....	1
Not at all.....	0

4. I can laugh and see the funny side of things:

As much as I always could.....	0
Not quite so much now.....	1
Definitely not as much now.....	2
Not at all.....	3

5. Worrying thoughts go through my mind

A great deal of the time.....	3
A lot of the time.....	2
From time to time but not too often..	1
Only occasionally.....	0

6. I feel cheerful:

Not at all.....	3
Not often.....	2
Sometimes.....	1
Most of the time.....	0

7. I can sit at ease and feel relaxed:

Definitely.....	0
Usually.....	1
Not often.....	2
Not at all.....	3

8. I feel as if I am slowed down:

Nearly all the time.....	3
Very Often.....	2
Sometimes.....	1
Not at all.....	0

9. I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all.....	0
Occasionally.....	1
Quite often.....	2
Very often.....	3

10. I have lost interest in my appearance

Definitely.....	3
I don't take so much care as I should..	2
I may not take quite as much care.....	1
I take just as much care as ever.....	0

11. I fell restless as if I need to be on the move:

Very much indeed.....	3
Quite a lot.....	2
Not very much.....	1
Not at all.....	0

12. I look forward with enjoyment to things:

As much as I ever did.....	0
Rather less than I used to.....	1
Definitely less than I used to.....	2
Hardly at all.....	3

13. I get sudden feelings of panic:

Very often indeed.....	3
Quite often.....	2
Not very often.....	1
Not at all.....	0

14. I can enjoy a good book or radio or TV programme:

Often.....	0
Sometimes.....	1
Not often.....	2
Very seldom.....	3

SECTION 2

Listed below are a number of symptoms you may or may not have felt since your stroke.

Tick 'YES' ☑ next to the symptoms you have experienced since your stroke

Tick 'NO' ☑ next to the symptoms you have not experienced since your stroke

Please also tick Yes or No if you believe these symptoms are related to your stroke.

	I have experienced this symptom since my Stroke		This symptom is related to my Stroke	
Pain	Yes ☐	No ☐	Yes ☐	No ☐
Sore Throat	Yes ☐	No ☐	Yes ☐	No ☐
Nausea	Yes ☐	No ☐	Yes ☐	No ☐
Breathlessness	Yes ☐	No ☐	Yes ☐	No ☐
Weight Loss	Yes ☐	No ☐	Yes ☐	No ☐
Fatigue	Yes ☐	No ☐	Yes ☐	No ☐
Stiff Joints	Yes ☐	No ☐	Yes ☐	No ☐
Sore Eyes	Yes ☐	No ☐	Yes ☐	No ☐
Wheeziness	Yes ☐	No ☐	Yes ☐	No ☐
Headaches	Yes ☐	No ☐	Yes ☐	No ☐
Upset Stomach	Yes ☐	No ☐	Yes ☐	No ☐
Sleep Difficulties	Yes ☐	No ☐	Yes ☐	No ☐
Dizziness	Yes ☐	No ☐	Yes ☐	No ☐
Loss of Strength	Yes ☐	No ☐	Yes ☐	No ☐
Forgetfulness	Yes ☐	No ☐	Yes ☐	No ☐

	I have experienced this symptom since my Stroke		This symptom is related to my Stroke	
Difficulty reading	Yes ☐	No ☐	Yes ☐	No ☐
Difficulty seeing	Yes ☐	No ☐	Yes ☐	No ☐
Difficulty speaking	Yes ☐	No ☐	Yes ☐	No ☐
Difficulty writing	Yes ☐	No ☐	Yes ☐	No ☐
Clumsiness	Yes ☐	No ☐	Yes ☐	No ☐
Tingling/numbness	Yes ☐	No ☐	Yes ☐	No ☐
Weakness	Yes ☐	No ☐	Yes ☐	No ☐
Paralysis	Yes ☐	No ☐	Yes ☐	No ☐
Getting upset or weepy	Yes ☐	No ☐	Yes ☐	No ☐

We are interested in your own personal views of how you view your stroke.
Please indicate how much you *agree or disagree* with the following statements about your stroke .

Please tick ☑ one box for each question.

VIEWS ABOUT YOUR STROKE					
My stroke will last a short time	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke symptoms are likely to be permanent rather than temporary	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke symptoms will last for a long time	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
The effects of my stroke will pass quickly	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
I expect to have the effects of my stroke for the rest of my life	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke is a serious condition	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke has major consequences on my life	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke does not have much effect on my life	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke strongly affects the way others see me	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke has serious financial consequences	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke causes difficulties for those who are close to me	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
There is a lot which I can do to control my stroke symptoms	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐

VIEWS ABOUT YOUR STROKE					
What I do can determine whether my stroke symptoms gets better or worse	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
The course of my stroke depends on me	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Nothing I do will affect my stroke symptoms	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
I have the power to influence my stroke symptoms	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My actions will have no affect on the outcome of my stroke symptoms	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke symptoms will improve in time	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
There is very little that can be done to improve my stroke symptoms	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My treatment will be effective in curing my stroke symptoms	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
The negative effects of my stroke can be avoided with therapy	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My therapy can control my stroke symptoms	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
There is nothing which can help my stroke	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
The symptoms of my stroke are puzzling to me	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke is a mystery to me	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐

VIEWS ABOUT YOUR STROKE					
I don't understand my stroke	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke doesn't make any sense to me	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
I have a clear picture or understanding of my stroke	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
The symptoms of my stroke change a great deal from day to day	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke symptoms come and go in cycles	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke symptoms are very unpredictable	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
I go through cycles in which my stroke gets better and worse	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
I get depressed when I think about my stroke	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
When I thing about my stroke I get upset	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke make me feel angry	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke does not worry me	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Having this stroke makes me feel anxious	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My stroke makes me feel afraid	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐

We are interested in what you think may have caused your stroke. As people are very different, there is no correct answer for this question. We are interested in your personal views about the factors that you think caused your stroke rather than what others including doctors or family may have suggested to you.

Below is a list of possible causes for your stroke. Please indicate how much you agree or disagree that they were the cause for your stroke.

Please tick ☑one box for each question

POSSIBLE CAUSES OF MY STROKE ARE:					
Stress or worry	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Hereditary- it runs in my family	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
A germ or virus	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Diet or eating habits	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Chance or bad luck	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Poor medical care in my past	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Pollution in the environment	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My own behavior	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My mental attitude (e.g. thinking about life negatively)	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Family problems or worries caused my stroke	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐

POSSIBLE CAUSES OF MY STROKE ARE:					
Overwork	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My emotional state (e.g. feeling down, lonely, anxious or empty)	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Ageing	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Alcohol	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Smoking	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Accident or injury	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
My personality	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐
Altered immunity	Strongly Disagree ☐	Disagree ☐	Neither agree nor disagree ☐	Agree ☐	Strongly Agree ☐

Please list in rank-order the three most important factors that you believe caused your stroke. You may use any of the items from the table above or you may have additional ideas of your own.

The three most important causes of my stroke for me are:

1. _____
2. _____
3. _____

List in order or importance

SECTION 3

These are some questions about your ability to look after yourself. They may not seem to apply to you, but please answer them all. Tick ☑ one box only in each group of questions

1. BATHING…In the bath or shower do you:
   - manage on your own? ☐
   - need help getting in and out? ☐
   - need other help? ☐
   - never have a bath or shower? ☐
   - need to be washed in bed? ☐

2. STAIRS…Do you climb stairs at home:
   - without any help? ☐
   - with someone carrying your frame? ☐
   - with someone encouraging you? ☐
   - with physical help? ☐
   - not at all? ☐
   - don't have stairs? ☐

3. DRESSING…Do you get dressed:
   - without any help? ☐
   - just with help with buttons? ☐
   - with someone helping you most of the time ☐

4. MOBILITY…Do you walk indoors:
   - without any help apart from a frame? ☐
   - with one person watching over you? ☐
   - with one person helping you? ☐
   - with more than one person helping? ☐
   - not at all? ☐
   - or do you use a wheelchair independently (e.g. round corners)? ☐

5. TRANSFER…Do you move from bed to chair:
   - on your own? ☐
   - with a little help from one person? ☐
   - with a lot of help from one or more people? ☐
   - not at all? ☐

6. FEEDING…Do you eat food:
   - without any help? ☐
   - with help cutting food or spreading butter? ☐
   - with more help? ☐

7. TOILET USE…Do you use the toilet or commode:
   - without any help? ☐
   - with some help but can do something? ☐
   - With quite a lot of help? ☐

8. GROOMING…Do you brush your hair and teeth, wash your face and shave:

without help? ☐
with help? ☐

9. BLADDER...Are you incontinent of urine?
   never ☐
   less than once a week ☐
   less than once a day ☐
   more often ☐
   or do you have a catheter manage for you ☐

10. BOWELS...Do you soil yourself?
   never ☐
   occasional accident ☐
   all the time ☐
   or do you need someone to give you an enema ☐

1. Did anyone help you complete this questionnaire?

No ☐

Yes ☐ If yes, please answer the questions below

2. How were you helped?

Please tick as many as appropriate

a) Someone read out the questions ☐
b) Someone translated the questions (if English is not your first language) ☐
c) Someone discussed the questions with you ☐
d) Someone ticked the boxes ☐
e) The whole questionnaire was completed on the participant's behalf without consulting them ☐
f) Other (please specify):_____

When was this pack completed (dd/mm/yyyy): __ __/ __ __/ __ __ __ __

Please take a minute to ...

Flick through the booklet
and check that you have answered
<u>all</u> the questions

and return by post to:

Alexia Campbell Burton
School of Healthcare, Baines Wing
University of Leeds
Leeds, UK
LS2 9JT

What happens next?

As part of this study you will be sent another questionnaire in 2-3 months.

Thank you for your time and cooperation

Appendix D

HADS Licensing Permission

(b) If the Licensee shall at any time be in breach of any of the terms and conditions of this Agreement and if capable of being remedied, such breach is not remedied within 15 days of receipt of written notice thereof; or

(c) If the Licensee is declared insolvent or bankrupt or goes into liquidation (other than voluntary liquidation for the purpose of reconstruction only) or if a Receiver is appointed or if the Licensee is subject to any similar event anywhere in the world.

Termination shall be without prejudice to any monies which may be due to the Publishers from the Licensee and without prejudice to any claim which the Publishers may have for damages and/or otherwise.

Upon termination of this Agreement for any reason the Licensee shall immediately cease to use the Material.

15. This Agreement constitutes the entire agreement between the parties in respect of the Material and supersedes all prior oral or written proposals, agreements or undertakings concerning the same.

16. This Agreement shall not be amended or modified in any way other than by an agreement in writing and signed by both parties or their duly authorised representatives and shall come into effect on receipt of the payment in full as specified above and a counter-signed copy of this Agreement.

17. This Agreement shall be governed by and construed in all respects in accordance with English Law and the courts of England and Wales shall have exclusive jurisdiction to settle any dispute arising out of or in connection with this Agreement, its subject matter and formation, including non-contractual disputes or claims.

AS WITNESS THE HANDS OF THE PARTIES
hereto the day and year first above written

Signed on behalf of GL Assessment Limited

8/3/2012

Signed by the Licensee: ***Please print this page, sign, and attach this signature page as a scanned document along with your typed User Agreement form, sent as a Word doc*** *and email to : permissions@gl-assessment.co.uk*

User's Signature (handwritten):	**Company/Organisation Stamp (if applicable):**
Title: PhD Student Researcher Company/Organisation: University of Leeds Date: March 6, 2012	

Appendix E

Participant Information Sheet
Version 1.2, July 1, 2011
Anxiety After Stroke

Invitation
You are invited to take part in a PhD research study about stroke survivors and the experience of worry and anxiety. This research is being conducted by researchers from the University of Leeds. Before you decide if you want to take part in this study, please take time to read this sheet carefully. If you wish please discuss it with your friends, family or GP. Please ask me if there is anything that you are not clear about, or if you would want more information. Take as much time as you need to decide if you wish to take part or not.

Why is this research being done?
For many people, having a stroke can be a frightening event. As a result, some people have a difficult time adjusting to life after stroke. This study wants to learn about the attitudes and beliefs you have about your stroke, and to see if these attitudes and beliefs are linked to levels of worry or fear.

Why have I been chosen?
You have been approached because your consultant has indicated that you have had a stroke. We hope to recruit 90-110 patients into this study over the next few months. It is expected that the study will include a cross-section of stroke survivors varying in age, gender, background and so forth who are willing to share their views.

Do I have to take part?
No. You decide if you want to take part or not. If you decide to take part you are free to withdraw at any time without giving a reason. This will not affect the care or treatment you receive. Neither will it affect your ability to access any services.

What if I change my mind and decide I don't want to take part in this study after I gave consent?
If you have consented to taking part in this study and then change your mind and feel you no longer want to take part you can contact Alexia Campbell Burton (the Chief Investigator) and let her know of your decision. You can contact the chief investigator by phone at 01133437185, by email at hccac@leeds.ac.uk , or by writing to address at the end of this information sheet. When you contact Alexia please remember to let her know if you want the information you have already provided to be included in the study or if you would like for it to be removed.

What will I be asked to do?
You will be asked to complete a consent form three questionnaires. The researcher will conduct the 1st one with you today, and you can take the 2nd one home with you. You will be asked to return the questionnaire using the FREEPOST envelope within the next TWO weeks. The last questionnaire will be sent to you in about three months to see how your views may have changed. You are not required to purchase a stamp to return any of the questionnaires.

Are there any disadvantages

The questionnaire will take about 30 minutes of your time.

Are there any risks of taking part?
Some questions in the package ask about your feelings. There is a very small chance that you may find this hard to deal with. If this happens take a break from answering the questions. You can start again when you feel better, or move on to another section of the package. You do not have to answer any questions that you find upsetting.

Advantages of taking part
The information you provide will help us understand the beliefs and attitudes of people after stroke . It will also help us understand how these beliefs and attitudes are linked to emotions and worry. Even if you are not anxious or worried the information you provide will still be valuable. It will be useful for health professionals and the NHS in helping them plan services for people after stroke.

What will happen to the results of the study?
The results from this study will form a significant portion of a PhD research project being conducted at the University of Leeds, School of Healthcare. We may also publish an article in a professional journal, and present findings at health related conferences. A version of the report for lay people (people who are not healthcare professionals or academics) will be produced and distributed to local stroke clubs and the UK Stroke Association. A copy of the lay report can be sent to you if you would like one when it becomes available.

Funding
This research is funded by a PhD Studentship award from the University of Leeds. None of the researchers on this project is being paid to enrol people into this study.

What do I have to do now?
You will be asked to sign a consent form. This will show that you agree to participate in this study. After this the researcher is going to ask you a few short questions today. You will be given a participant package with another questionnaire. Please take it home with you and complete it in the next two weeks. Mail it back in the freepost envelope you have been provided.

Contact for further information

CHIEF INVESTIGATOR
Alexia Campbell Burton
School of Healthcare
University of Leeds
Leeds, UK LS2 9JT
Tel: 0113 343 7185
hccac@leeds.ac.uk

SUPERVISOR
Dr Felicity Astin
School of Healthcare
University of Leeds
Leeds, UK LS2 9JT
Tel: 0113 343 7558
f.astin@leeds.ac.uk

Thank you for taking the time to read this information sheet

Appendix F

Reference ID:						

UNIVERSITY OF LEEDS

Anxiety After Stroke

Patient Consent Form

Version 1.2

Please initial the boxes

1. I have read and understand the Information Sheet (Version 1.2 dated July 1, 2011) for the above study and have had the opportunity to ask questions. ☐

2. I understand that taking part is voluntary and I am not required to answer any questions I am uncomfortable with. I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected. ☐

3. I understand that even if I withdraw from the above study the data already collected from me will be used in analysing the study, unless I specifically withdraw consent for this. I understand that my identity will remain anonymous. ☐

4. I understand that my name, address, telephone number, and information about the type of stroke I had will be accessed by a member or my care team or the chief investigator for the purposes of this research study. ☐

5. I agree for my name, address, telephone number, and information about the type of stroke I had to be stored at the School of Healthcare, University of Leeds for the purpose of this study. ☐

6. I understand that a copy of this Consent Form will be stored at the School of Healthcare, University of Leeds ☐

7. I agree to take part in the above study. ☐

PARTICIPANT:

Participant Name:	Date:	Signature:

Witness (to be completed if the participant is unable to sign for themselves):

Name of witness::	Date:	Signature:

Lead Researcher (Signed by Chief Investigator):

Name of Lead Researcher:	Date:	Signature:

CONTACT DETAILS:

Researchers: Alexia Campbell Burton/ Dr Felicity Astin
Telephone Number: 01133437185
Email: hccac@leeds.ac.uk
ADDRESS: University of Leeds, Baines Wing Room 3.35, Leeds, UK LS2 9JT

(1 copy for the participant, 1 copy to be stored with the Lead Researcher at the School of Healthcare, University of Leeds)

Appendix G

NHS
National Research Ethics Service
Leeds (East) Research Ethics Committee
Yorkshire and Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050108

Mrs C. Alexia Campbell Burton
University of Leeds, School of Healthcare
Baines Wing, PhD Suite Room 3.35
Leeds, UK
LS2 9JT

21 February 2011

Dear Mrs Campbell Burton

Study Title: **Anxiety After Stroke: Prevalence, Intervention Effectiveness, and Illness Representations**
REC reference number: **11/H1306/6**
Protocol number: **n/a**

Thank you for your letter of 16 February 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Protocol	1.0	10 January 2011
Response to Request for Further Information		16 February 2011
Investigator CV		
6CIT		
Poster		
Participant Information Sheet	1.1	11 February 2011
Questionnaire: Validated - Assessment Package	1.0	10 January 2011
Evidence of insurance or indemnity		12 January 2011
REC application		11 January 2011
Participant Consent Form	1.1	11 February 2011
Participant Details		
MCA Certificate		15 February 2011
CV - P KNAPP		
CV - J MURRAY		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators

- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/H1306/6	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Prof Alan Ebbutt
Vice Chair

Email: jade.thorpe@leedspft.nhs.uk

Copy to: *Mrs Rachel E de Souza*

Barnsley Hospital NHS
NHS Foundation Trust

Gawber Road
Barnsley
S75 2EP

Tel: 01226 730000
Fax: 01226 202859
Minicom: 01226 321014

Research and Development Directorate

email: michael.bramall@nhs.net

Research Governance Office
Barnsley Hospital NHS Foundation Trust
Tel: 01226 730000
Extension: 2348
Fax: 01226 208159

04 March 2011

Mrs C. Alexia Campbell Burton
University of Leeds
School of Healthcare
Baines Wing
PhD Suite Room 3.35
LS2 9JT

Dear Mrs Campbell Burton

Study Title: **Anxiety after stroke: Prevalence, Intervention Effectiveness, and Illness Representations**

REC Ref: **11/H1306/6**

Thank you for submitting the above project for approval by Barnsley Hospital NHS Foundation Trust. The project was considered by the Research Governance Committee of Barnsley Health and Social Care Research and Development Alliance at a meeting and I am pleased to confirm that the committee agreed to approve the project.

The Documents received and approved were:

Document	*Version*	*Date*
Protocol	1.0	10 January 2011
6CIT test		
Poster		
Participant Information Sheet	1.1	11 February 2011
Questionnaire Assessment Package	1.0	10 January 2011
Evidence of Insurance or Indemnity		12 January 2011
R&D Checklist		
Patient Consent Form	1.1	11 February 2011
Participant Details Form		
MCA Certificate		15 February 2011
CV - C.A Campbell Burton		
CV - P Knapp		
CV- J Murray		
Nhs SSI Form - Barnsley		
Nhs REC Form		
Sponsorship letter		21 January 2011
Supervisor Letter		4 January 2011
Response to request for further Information		16 February 2011

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Ref: **HC 1546 (Research)**

Miss Carla Alexia Campbell Burton
237 Granary Wharf
Watermans Place
Leeds
LS1 4GQ

Human Resources Department
Clocktower
Northern General Hospital
Sheffield
S5 7AU

Please ask for: Laura Tufnell
Telephone: (0114) 30 52504
E mail Laura.Tufnell@sth.nhs.uk

Dear Miss Campbell Burton

HONORARY CONTRACT

I am instructed by the Sheffield Teaching Hospitals NHS Foundation Trust to offer you an honorary appointment as a Research Student in the Stroke Unit, under the supervision of Dr DaCosta at the Northern General Hospital, commencing on the **1 July 2011** to the **30 November 2011**.

This Honorary Contract is not a contract of employment and confers no employment rights or entitlements except the rights of access to patients, notes and hospital premises within the remit of the Sheffield Teaching Hospitals NHS Foundation Trust. It is subject to you maintaining the strictest confidentiality of information with which you may come into contact during the course of your appointment, maintaining acceptable standards of conduct and that you make yourself familiar with the relevant policies and procedures of the Trust and specifically in relation to Health and Safety and Fire. Failure to abide by these provisions will result in this authorisation being withdrawn.

As a contract holder of Sheffield Teaching Hospitals NHS Foundation Trust you must comply will all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance.

Attending an occupational health appointment with the Trust may be a requirement of the clearing process. This appointment enables the Occupational Health Department to ensure that any health risks posed to you, patients and employees of the Trust are reviewed and addressed accordingly. This contract is conditional on you attending this appointment if requested to do so by the Occupational Health Department.

This honorary contract is subject to a confidential annual review to assess all aspects of your work and progress.

The Sheffield Teaching Hospitals NHS Foundation Trust accept no responsibility for the damage to or loss of personal property, with the exception of small valuables handed to their officials for safe custody. You are, therefore, recommended to take out an insurance policy to cover your personal property.

Notwithstanding the above, you will be treated in accordance with Trust employees, for the purpose of employment insurance (and for no other purposes) during the proper performance of your duties, provided that at all times you exercise all reasonable skills and judgment and always act in good faith.

Appendix H

PARTICIPANT DETAILS

The following sheet outlines the baseline data Elements that will be collected directly from participants or from the participant's file after consent has been obtained. This information will be stored on a password protected University of Leeds computer. The hard copy will be stored in a locked filing cabinet at the University of Leeds.

The Chief Investigator will ask participants to answer the following questions:

Participant Details:

Title	
First Name	
Last Name	

Expected Place of Residence (within the next 3 months)

Address line 1	
Address line 2	
Postcode	
Telephone number (home or mobile)	

Sex of Participant:

Male	
Female	

Date of Birth_____

Did participant live alone before the stroke?

Yes	
No	

Ethnicity

White- British	
Any other White Background	
Mixed- White and Black Caribbean	
Mixed- White and Black African	
Mixed- White and Asian	
Any other Mixed background	
Asian- Bangladeshi	
Asian- Indian	
Asian- Pakistani	
Black- Caribbean	
Black-African	
Any other Black Background	
Chinese	
Other	
Not stated	

Comorbidities

1. Have you ever had a heart attack? Yes___ No___

2. Have you ever been treated for heart failure? (You may have been short of breath and the doctor may have told you that you had fluid in your lungs) Yes___ No___
3. Have you had an operation to unclog or bypass the arteries in your legs? Yes___No_
4. Do you have Asthma? Yes___NO___
   If Yes: Do you take medicines for your asthma?
   Yes (only with flare ups)___ Yes (takes medicine regularly even when not flaring up)_
5. Do you have emphysema, chronic bronchitis or chronic obstructive lung disease? Yes__No__
   If Yes, do you take medicines for your lung disease?
   Yes (only with flare ups)___ Yes (takes medicine regularly even when not flaring up)_
6. Do you have stomach ulcers, or peptic ulcer disease? Yes___ NO___
7. Do you have diabetes? Yes___ NO___
8. Do you have problems with your kidneys? Yes___ No___
9. Do you have rheumatoid arthritis? Yes___ No___
10. Do you have cirrhosis or serious liver damage? Yes___ No___
11. Do you have cancer? Yes___ No___

The following information will be retrieved from the patient file

Date of 1st Stroke:_____

Pathological classification of 1st stroke:

Cerebral Infarction	
Primary Intracerebral Haemorrhage	
Subarachnoid Haemorrhage	

Clinical Classification of stroke symptoms

Total Anterior Circulate Stroke (TACS)	
Partial Anterior Circulate Stroke (PACS)	
Lacunar Stroke (LACS)	
Posterior Circulation Stroke (POCS)	

Does patient have history of anxiety or depression (if yes when)_____

Is the patient receiving treatment for anxiety or depression? (Describe whether pharmaceutical or psychological, and when it was started)_____

Reference ID:					

6CIT

The 6CIT is a test for cognitive impairment. It is assumed that all participants have capacity to participate in research regardless of the score on the test. It will only be

Has the patient given verbal consent for the 6CIT to be conducted, ☐ Yes ☐ No
or has verbal carer assent been obtained

Before carrying out this test, make sure that the patient is wearing their glasses and/or their hearing aid. Check that patient can hear you.

Enter 0 if the patient answered the question correctly. If the patient answered the question incorrectly then the number or errors will be recorded. Score 1 for each incorrect response. The maximum number or errors is stated in the table for each question. For questions with more than one error state the maximum number or errors attained.

	Max error	Score		Weight		Weighted Score
1. What Year is it now	1		X	4	=	
2. What Month is it now	1		X	3	=	
Memory Phrase- repeat after me John/Brown,/42/ West Street, / Bedford						
3. About what Time is it? (within 1 hour)	1		X	3	=	
4. Count backwards 20 to 1	2		X	2	=	
5. Say the months in reverse order	2		X	2	=	
6. Repeat the memory phrase	5		X	2	=	

Appendix I

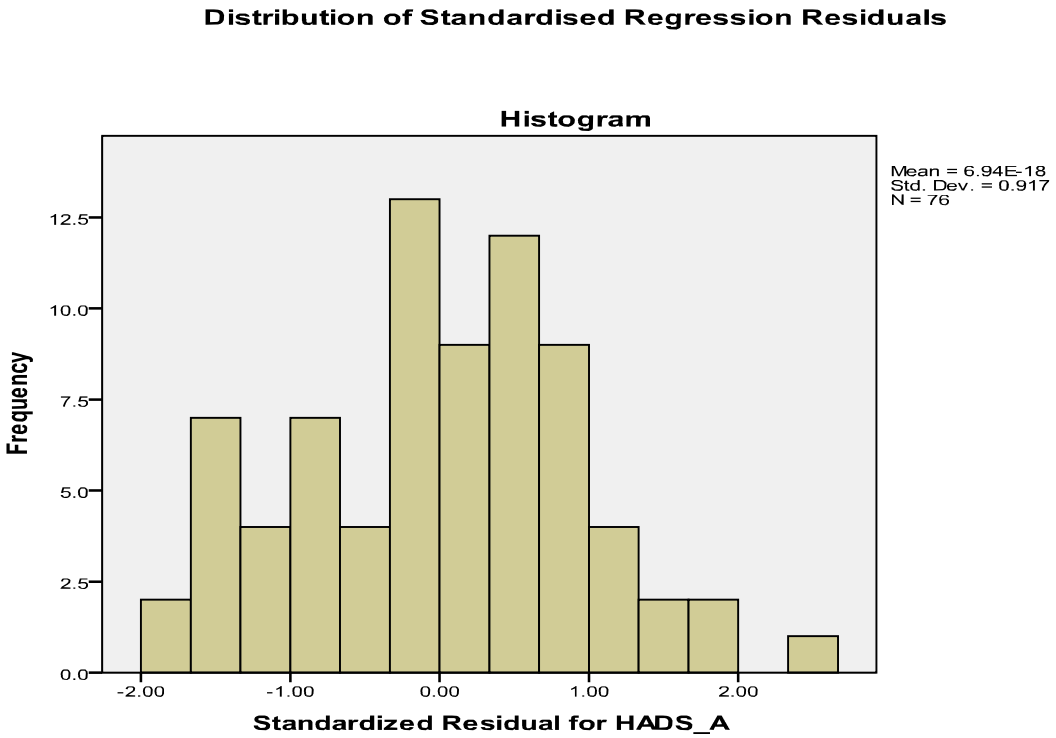
Levene's Test of Equality of Error Variances[a]

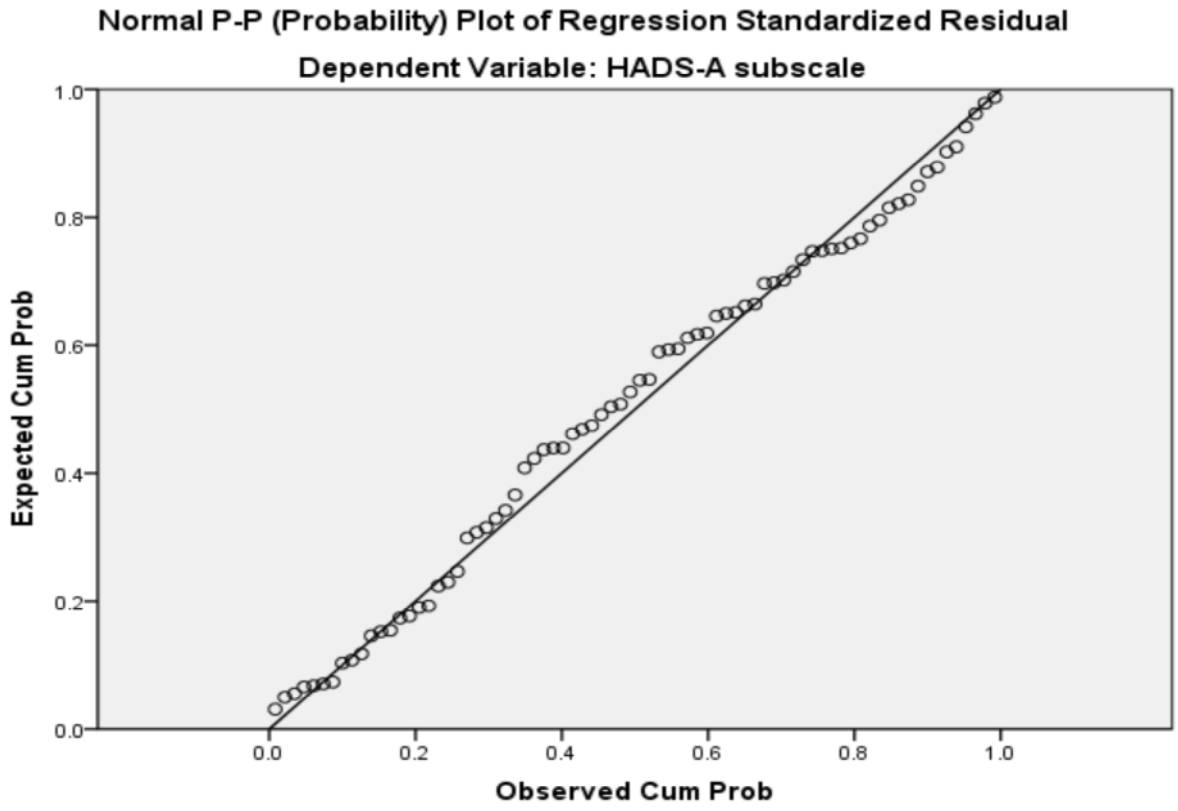
	F	df1	df2	Sig.
Identity	.024	2	73	.977
Timeline	.564	2	73	.572
Cyclical	1.003	2	73	.372
Consequences	.965	2	73	.386
Personal control	.528	2	73	.592
Treatment control	.374	2	73	.689
Coherence	1.360	2	73	.263
Emotional	1.815	2	73	.170

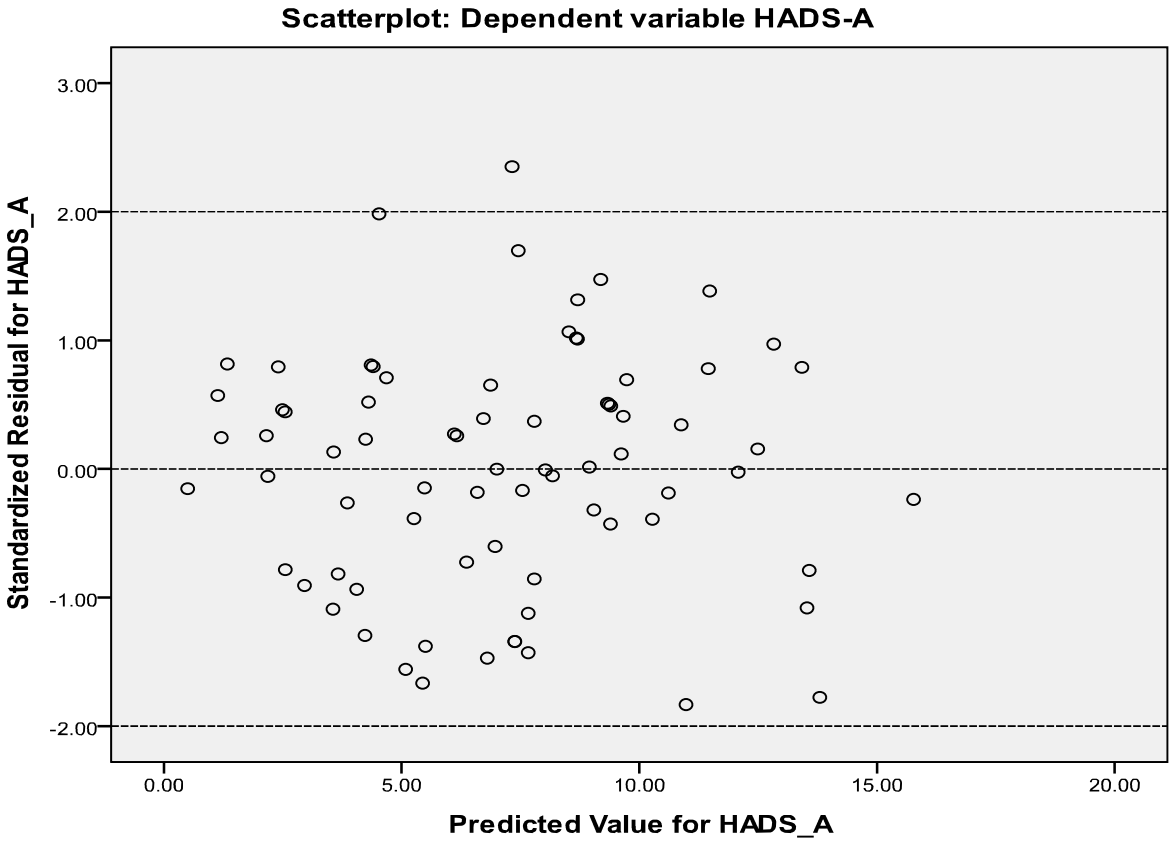
Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a. Design: Intercept + Anx_Dep_11

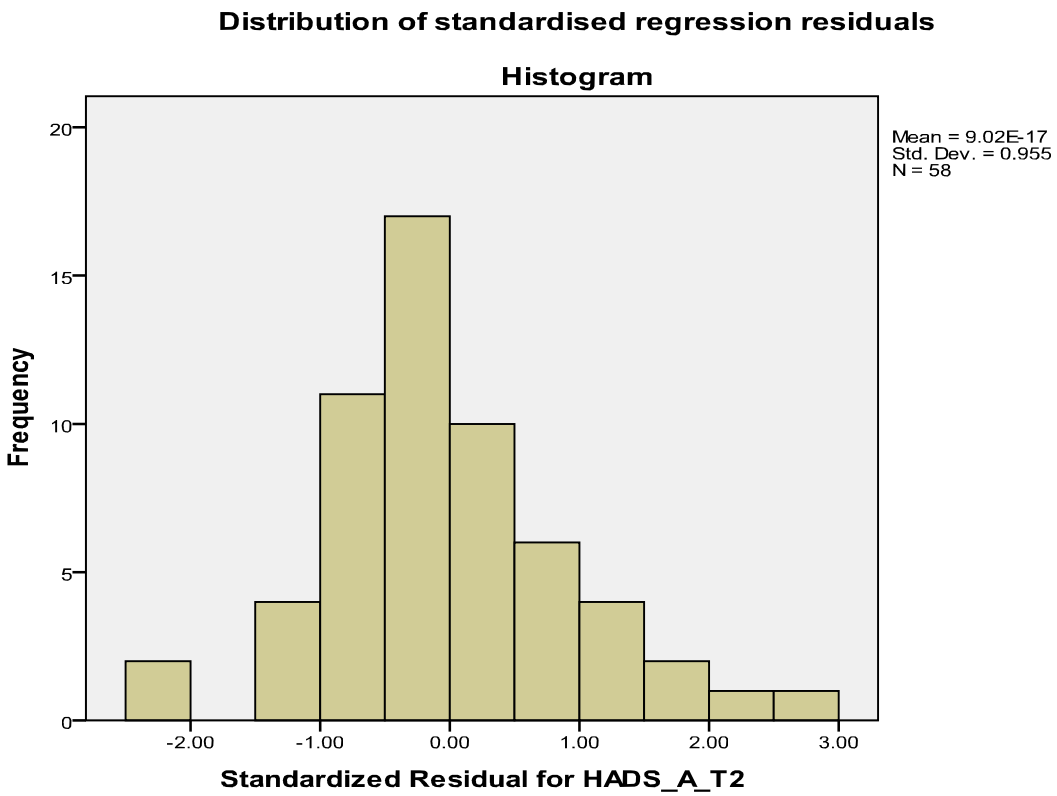
Baseline regression model diagnostic plots

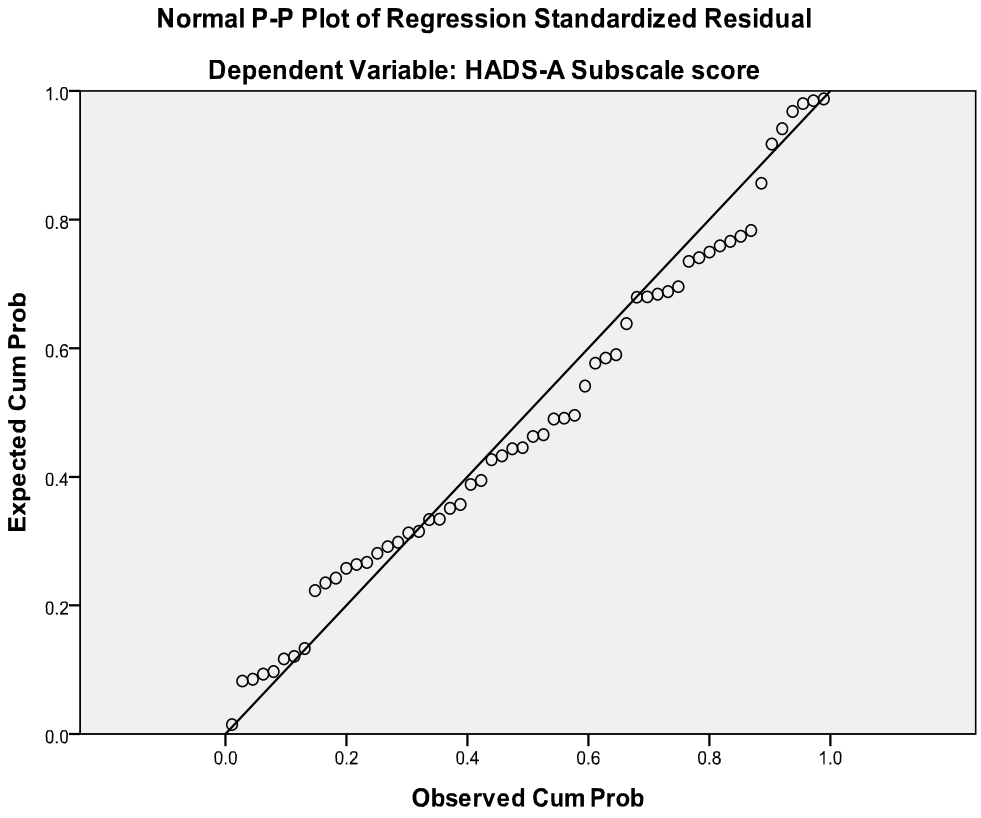


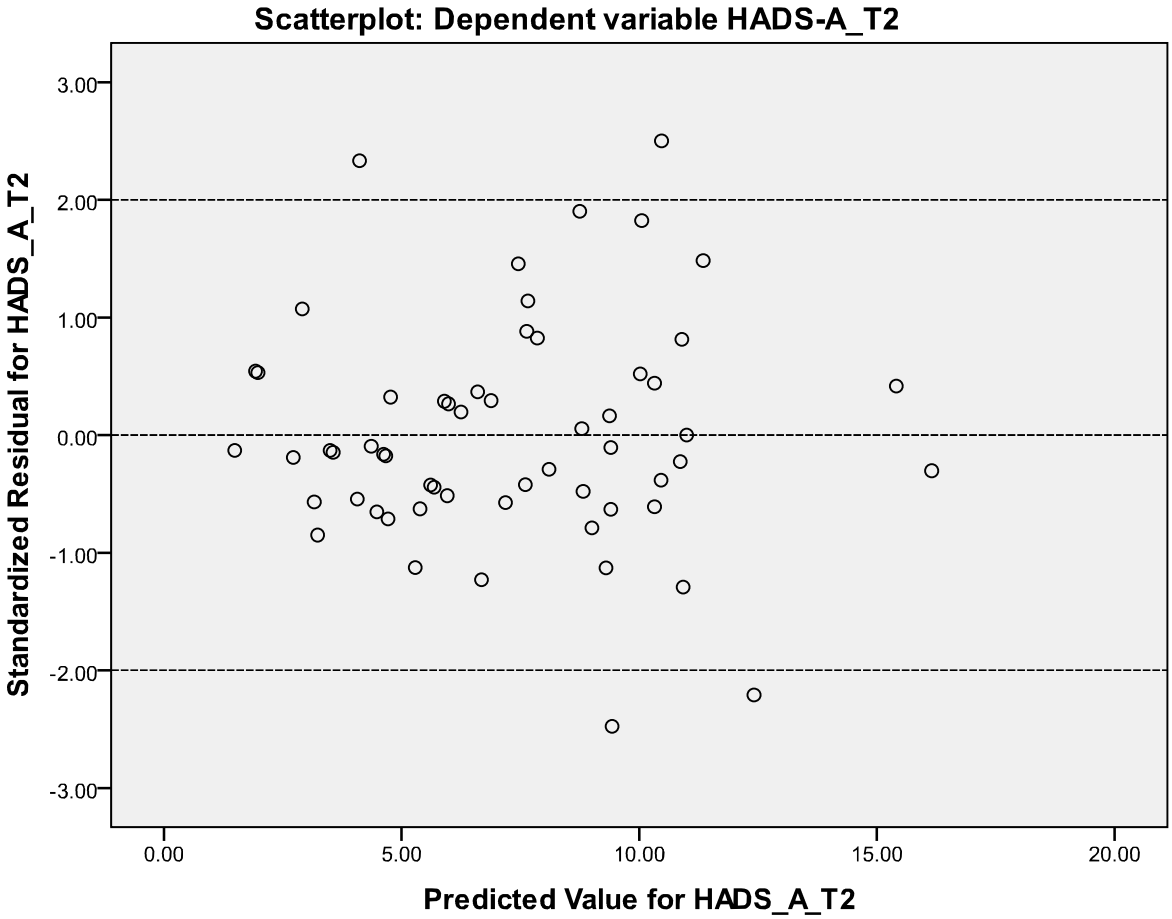

Normal P-P (Probability) Plot of Regression Standardized Residual
Dependent Variable: HADS-A subscale
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0


Scatterplot: Dependent variable HADS-A
Standardized Residual for HADS_A
Predicted Value for HADS_A
3.00
2.00
1.00
0.00
-1.00
-2.00
0.00
5.00
10.00
15.00
20.00

Longitudinal Regression Diagnostic plots






Scatterplot: Dependent variable HADS-A_T2
Standardized Residual for HADS_A_T2
3.00
2.00
1.00
0.00
-1.00
-2.00
-3.00
0.00
5.00
10.00
15.00
20.00
Predicted Value for HADS_A_T2