Fatigue after stroke: its frequency, natural history and associations with mood, physical activity and physical fitness

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Declaration

I declare that I composed this thesis by myself.

I declare that all of the material presented in this thesis is my own work, except where stated otherwise in the section below and in the relevant sections of this thesis.

The work has not been submitted for any other degree or qualification

I declare that the included publications are my own work, except where stated otherwise in the section below.

Signed:

Date:

Contributions by others

Dr Simeo Wu contributed by doing the double data extraction for one of the systematic reviews.

Dr Mansur Kutbaev contributed by doing the double data extraction for the other systematic review, working out NIHSS scores from outpatient's notes, double checking that the Oxford Classifications which I had taken from patient notes were consistent with their electronic notes and by very kindly recruiting three participants for the longitudinal study whilst I was on annual leave.

The longitudinal cohort study was designed by Professor Gillian Mead with help from Professor Martin Dennis, Professor Alasdair MacLullich, Dr Susan Lewis, Dr Carolyn Greig, and Professor Michael Sharpe.

Dr Susan Lewis either carried out or advised on the appropriate statistics for some of the analyses in Chapter 4 (and therefore one of the included publications).

Professor Gordon Murray advised on the appropriate statistics in Chapter 5 (and therefore one of the included publications) and the statistical analysis that he suggested was then carried out by Dr Susan Lewis.

Professor Gillian Mead significantly helped with the writing of the final versions of the publications which are included in this thesis.

Abstract

Background: Fatigue is common and distressing after stroke. Many stroke survivors say it is their worst or one of their worst symptoms. The frequency of clinically significant fatigue, whether fatigue is likely to be more or less problematic over time, and its aetiology are unknown. There are currently no known treatments. One hypothesis is that fatigue after stroke is triggered by physical deconditioning which sets up a self-perpetuating cycle of fatigue, avoidance of physical activity, further deconditioning and more fatigue. Another theory is that low mood may contribute to fatigue.

Aims: This thesis therefore aims to investigate the frequency and natural history of fatigue after stroke and to explore its associations with mood, physical activity and/or fitness.

Method: These aims were addressed by carrying out: 1) a systematic review of all longitudinal observational studies which have assessed fatigue on at least two separate time points and reported its frequency, 2) a systematic review of all observational studies which have measured both fatigue poststroke and one or more measures of physical activity and/or fitness at the same time point and 3) a longitudinal cohort study which assessed clinically significant fatigue, mood and physical activity and fitness at one, six and 12 months after stroke.

Results: Frequency of fatigue ranged from 30% to 92% at first time point and frequency of fatigue decreased over time in seven of the ten studies identified in the systematic review of longitudinal studies. The second systematic review found that only two of the eight studies identified found a significant direct relationship between fatigue and physical activity and/or fitness poststroke. In the longtidudinal cohort study, clinically significant fatigue was identified in 32.6% of 132 participants at one month and was still present in a fifth of 91 participants at 12 months, two-thirds of participants who had clinically significant fatigue at one month did not have it by six months and that most (60.4%) individuals either reported fatigue at all three time points or that they did not have fatigue at any time point. There were significant associations between daily step count and fatigue at each time point (p=<0.0001, 0.011, 0.006). Physical activity (p=0.002, 0.006) and anxiety (p=<0.0001, 0.001) at one month were independent significant predictors of fatigue severity at six and 12 months after stroke. Age, gender, fatigue before stroke, step count and anxiety at one month accounted for 22% and 27% of the variance in fatigue severity at six and 12 months respectively. No significant associations were found between fatigue and measures of physical fitness.

Discussion and conclusion: The findings suggest that although fatigue is common and persistent after stroke, it is more likely to become less problematic over time. They also suggest that the de-conditioning hypothesis of the aetiology of fatigue may be too simplistic and that other factors are involved in the development and perpetuation of fatigue after stroke. Implications are that patients should be assessed for fatigue early after stroke and that the development of an intervention which increases activity and/or reduces anxiety may be beneficial.

Lay Summary

Many people feel very tired after stroke and find this tiredness to be very upsetting. Many stroke survivors say it is their worst or one of their worst symptoms and is a problem for them as it interferes with their everyday activities. However it is not known how many experience a problematic tiredness, how long it lasts or whether it gets better or worse over time. It is also not known what causes this tiredness and currently there are no known treatments. One theory is that stroke survivors don't do enough exercise after their stroke which leads to their muscles becoming weaker. This means it requires extra effort to carry out everyday tasks and this causes tiredness. They then do even less exercise which leads to their muscles getting even weaker which leads to even more tiredness. Another theory is that mood problems such as depression may contribute to this tiredness.

Therefore this thesis attempted to find out:

- How many stroke survivors have a problematic tiredness?
- How long this tiredness lasts for and whether it gets better or worse?
- Whether there a relationship between problematic tiredness and mood problems?
- Whether there a relationship between physical activity and/or physical fitness and problematic tiredness?

This thesis attempted to answer these questions by:

- Searching databases to find all studies that have previously measured tiredness in the same stroke survivors at more than one time point and to find all studies which have previously measured tiredness and aspects of physical activity and/or physical fitness at the same time point.
- Carrying out a study which measured tiredness, mood, physical activity and physical fitness in the same stroke patients at one, six and 12 months after their stroke.

Results

The percentage of people who reported tiredness ranged from 30% to 92% at first time point and this percentage decreased over time in seven of the ten studies identified in the review of previous studies which had measured tiredness at more than one time point. The second review of previous studies found that only two of the eight studies identified found a relationship between tiredness and physical activity and/or physical fitness after stroke. In the third study, problematic tiredness was found in 32.6% of stroke survivors at one month and was still present in a fifth at 12 months, two thirds of participants who had problematic tiredness at one month did not have it by six months and most (60.4%) individuals either reported tiredness at all three time points or that they did not have tiredness at any time point. Daily step count and tiredness were related to each other at each time point. Participants who did less steps per day and who were more anxious at one month were more likely to be tired at six and 12 months after stroke. However the results also suggested that step count and anxiety were not the only factors which were

contributing to tiredness. No relationship was found between tiredness and measures of physical fitness.

Discussion and conclusion

This thesis has found that problematic tiredness is common after stroke and that although some people remain tired for several years after their stroke, tiredness is more likely to become less problematic over time. The results suggest that the theory that weak muscles (due to lack of activity) cause tiredness after stroke may be too simple. It is likely that other factors are involved. Implications are that stroke patients should be assessed for tiredness early after their stroke and the development of a treatment which increases physical activity and/or reduces anxiety levels may be helpful.

Publications arising from the work presented in this thesis

Wu S., Duncan F., Anderson N.H., Kuppuswany A., Macleod M.R. and Mead G.E. (2015) Exploratory study of associations between serum C-reactive protein and fatigue after stroke. *PLoS One*. 10(11), e0143784.

Duncan F., Lewis S.J., Greig C.A., Dennis M.S., Sharpe M., MacLullich A.M.J. and Mead G.E. (2015) Exploratory longitudinal cohort study of associations of fatigue after stroke. *Stroke*. 46, pp 1052-1058.

Tieges Z., Mead G., Allerhand M., Duncan F., van Wijck F., Fitzsimons C., Greig C. and Chastin S. (2015) Sedentary behaviour in the first year after stroke: a longitudinal cohort study with objective measures. *Archives of Physical Medicine and Rehabilitation.* 96 (1), pp 15-23.

Duncan, F., Greig C., Lewis S., Dennis M., MacLullich A., Sharpe M. and Mead G. (2014) Clinically significant fatigue after stroke: a longitudinal cohort study. *Journal of Psychosomatic Research.* 77(5), pp 368-373.

Kutlubaev, M.A., Shenkin, S.D., Farrall, A.J., Duncan, F.H., Lewis, S.J., Greig, C.A., Dennis, M.S., Wardlaw, J.M., MacLullich, A.M.J. and Mead, G.E. (2013) CT and Clinical Predictors of Fatigue at One Month After Stroke. *Cerebrovas Diseases Extra*. 3(1), pp 26-34.

Duncan, F., Wu, S. and Mead, G. (2012) Frequency and Natural History of Fatigue After Stroke: A Systematic Review of Longitudinal Studies. *Journal of Psychosomatic Research*. 73(1), pp 18-27.

Duncan, F., Kutlubaev, M., Greig, C., Dennis, M. and Mead, G. (2012). Fatigue After Stroke: A Systematic Review of Associations with Impaired Physical Fitness. *International Journal of Stroke.* 7(2), pp 157-62.

Conference presentations arising from the work presented in this thesis

Duncan, F., Wu S. and Mead G. *Frequency and Natural History of Fatigue after Stroke: A Systematic Review*. XXI European Stroke Conference, Lisbon, Portugal, 22nd – 25th May 2012.

Duncan F., Greig C.A., Lewis S.C., Dennis M.S., MacLullich A. and Mead G. *Fatigue is associated with reduced physical activity one month after stroke*. XXI European Stroke Conference, Lisbon, Portugal, 22nd – 25th May 2012.

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Contents

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Abbreviations

10MWT – 10 meter walk test

6MWT – Six Minute Walk Test

ANOVA – Analysis of Variance

BP – Blood Pressure

CBT – Cognitive Behavioural Therapy

CES-D – Center of Epidemiologic Studies- Depression Scale

CFS – Chalder Fatigue Scale

CFS – Chronic Fatigue Syndrome

CI – Confidence Interval

CIS – Checklist Individual Strength

CRF – Cancer Related Fatigue or Clinical Research Facility

CRP – C-Reactive Protein

EM – Expectation Maximisation

FAI – Fatigue Assessment Instrument

FAS – Fatigue Assessment Scale

FD – Fiona Duncan

FIS – Fatigue Impact Scale

FSMC – Fatigue Scale for Motor and Cognitive Functions

FSS – Fatigue Severity Scale

GAD – Generalised Anxiety Disorder

GET – Graded Exercise Therapy

GM – Gillian Mead

GP – General Practitioner

HADS – Hospital Anxiety and Depression Scale

HARS – Hamilton Anxiety Rating Scale

HDRS – Hamilton Depression Rating Scale

ICH – Intracerebral Haemorrhage

IQR – Interquartile Range

LACS – Lacunar Syndrome

LLEP – Lower Limb Extensor Power

MCAR – Missing Completely At Random

MFI-20 – Multidimensional Fatigue Inventory -20

MFIS – Modified Fatigue Impact Scale

MFSI-SF – Multidimensional Fatigue Symptom Inventory – Short Form

MK – Mansur Kutlubaev

MMSE – Mini Mental State Examination

MS – Multiple Sclerosis

MYS – Map Young Persons with Stroke

NFI-Stroke – Neurological Fatigue Index for Stroke

NHP – Nottingham Health Profile

NHS – National Health Service

NIHSS – National Institute of Health Stroke Scale

OR – Odds Ratio

PACS – Partial Anterior Circulation Syndrome

PASE – Physical Activity Scale for the Elderly

PD – Parkinson's disease

POCS – Posterior Circulation Syndrome

POMS – Profile of Mood States

PSF – Post-stroke Fatigue

PTSD – Post-traumatic stress disorder

RCT – Randomised Controlled Trial

SAH – Subarachnoid Haemorrhage

SD – Standard Deviation

SEM – Structural Equation Modelling

SF-36 – 36-item Short Form Health Survey

SPSS – Statistical Package for the Social Sciences

SW – Simeo Wu

TACS – Total Anterior Circulation Syndrome

TIA – Transient Ischemic Attack

UK – United Kingdom

VAS – Visual Analogue Scale

VIF – Variance Inflation Factor

Chapter 1 – Introduction to Thesis

Section 1 – The Problem of Stroke

Definition of stroke

"Stroke" is defined as:

"a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal, and at times global loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (Hatano, 1976, p541).

This definition includes ischaemic strokes which account for approximately 85% of all first ever strokes, intracerebral haemorrhages (ICH) which account for around 10% and subarachnoid haemorrhages (SAH) which account for about 5%. (Rothwell et al. 2004).

Epidemiology of stroke

Worldwide in 2010, 16.9 million people suffered a stroke, there were 5.9 million stroke-related deaths and there were 33 million living people who had experienced a stroke. In the same year in the UK, 146 000 people had a stroke, there were almost 60 thousand stroke-related deaths and there were almost 665 000 stroke survivors (Feigin et al. 2014).

Changes in stroke incidence, prevalence and mortality between 1990 and 2010

In the last two decades in the UK, there have been substantial changes in stroke incidence, prevalence and mortality (Table 1.1 and Table 1.2). Between 1990 and 2010 the absolute number of incident stroke decreased by 1.1% from 147 324 to 145 700 and, taking age into account, stroke incidence decreased by 19% from 141.97 incidents per 100 000 person-years to 115.40 incidents per 100 000 person-years. However as the decrease in the mortality rate during this time period was greater than the decrease in the incidence of stroke, the prevalence of stroke in the UK increased by 42% from 468 186 in 1990 to 664 871 in 2010 and the number of stroke survivors per 100 000 people in the UK increased by 16.6% from 506.64 in 1990 to 590.72 to 2010 (Feigin et al. 2014).

Table 1.1 - Absolute number of incident and prevalent strokes and mortality to incidence ratio in UK. (Adapted from Feigin et al. 2014, supplementary material)

	Prevalence	Incidence	Mortality to incidence ratio	Deaths
1990	468 186	147 324	0.57	82974
2010	664 871	145 700	0.41	59689

Table 1.2 - Age-standardised stroke incidence rates and mortality rates per 100 000 person-years and prevalence per 100 000 people in UK. (Adapted from Feigin et al. 2014, supplementary material).

	Prevalence	Incidence	Mortality
1990	506.64	141.97	71.20
2010	590.72	115.40	38.22

It may seem surprising that the absolute number of incident strokes has decreased when it is taken into consideration that age is a major factor for stroke (Sacco et al. 1997) and the UK population is getting older. The percentage of the UK population over 65 years old was 15% in 1985 and 17% in 2010. This was an increase of 1.7 million people (Office of National Statistics 2012). In addition, obesity is also a risk factor for stroke (Strazzullo et al. 2010) and in the last two decades the percentage of adults in the UK who were obese increased from 13.2% in 1993 to 24.4% in 2012 for men and from 16.4% to 25.1% for women (Health and Social Care Information Centre 2014). However although the age and obesity levels of the population have been increasing, in the last two decades there have been several improvements in the primary prevention of stroke. For instance, there have been improvements in the effectiveness of anti-hypertensive medication and changes in the treatment of other risk factors such as high cholesterol, diabetes and atrial fibrillation (Donnan 2008). In addition the percentage of people in the UK who smoke cigarettes has substantially decreased from 46% in 1974 to 19% in 2013 (Office of National Statistics 2013).

The lower death rate from stroke over the past 20 years could be explained by the improvements in the management of acute stroke. For instance, the introduction of specialist acute stroke units have been reported to decrease mortality by 20% relative to a general hospital ward (Donnan 2008; Langhorne et al. 1993).

Changes in stroke incidence, prevalence and mortality in the future

The UK population is estimated to get even older in the next few years. It is estimated that by 2035, 23% of the UK population will be aged 65 and over and 5% will be aged 85 and over (Office of National Statistics 2012) which means that, depending on the degree to which primary prevention and acute stroke management continue to improve, the number of stroke survivors in the UK is likely to continue to increase in the future.

Stroke as a long term chronic disease

Many of these stroke survivors will live for years and not fully recover which means that stroke should be viewed as a long term chronic illness as well as an acute serious illness. Approximately half of all stroke survivors will have a disability at one year after stroke onset (Paul, Srikanth and Thrift 2007) and 36% of all stroke survivors will still be disabled after five years (Brainin et al. 2011). Disabilities occur as a consequence of the numerous impairments that are associated with having a stroke. Some of the most common impairments that are experienced by stroke survivors include limb weakness, visual problems, slurred speech, reduced bladder control, swallowing problems, aphasia, sensory loss, inattention/neglect and reduced consciousness (Lawrence et al. 2001) (Table 1.3).

Table 1.3 - Prevalence of acute impairments in first ever stroke patients (Adapted from table in Lawrence et al. 2001).

Impairment	Percentage of stroke survivors who are affected.
Upper limb motor deficit	77%
Lower limb motor deficit	72%
Urinary incontinence	48%
Reduced consciousness	45%
Dysphagia	45%
Dysarthria	42%
Upper limb sensory deficit	30%
Lower limb sensory deficit	27%
Visual field defect	26%
Dysphasia	23%
Visual neglect	20%
Sensory inattention	19%
Gaze paresis	18%

Each of these impairments can have a profound effect on many aspects of a stroke survivor's life in the medium to long term. For instance, they may lead to the stroke survivor having difficulty with walking, talking, dressing, eating, washing, toileting, continence, participating in their usual leisure activities or returning to employment.

It is estimated that between 25% and 50% of all stroke survivors may require help for activities of daily living. (Gordon et al. 2004).

These impairments are usually directly caused by the stroke, however stroke can also directly or indirectly contribute to a number of complications and many of these complications are hidden. Common hidden complications of stroke include pain, depression, anxiety, emotionalism and cognitive problems and dementia (Table 1.4). Each of these complications can have a long term impact on a stroke survivor. For instance depression can have a detrimental effect on recovery, anxiety can lead to a lack of engagement in social activities due to a fear of falling or embarrassment, emotionalism, where a stroke survivor either laughs or cries without explanation and often in inappropriate situations, can lead to embarrassment and distress and cognitive problems can result in the stroke survivor having a reduced ability to carry out daily activities (van Wijck 2013).

Table 1.4 - Frequency of hidden post-stroke complications.

Complication	**Percentage of stroke survivors who are affected**
Depression	33% up to six months post-stroke 34% six months or more post-stroke (Hackett et al. 2005)
Anxiety	20% in the acute phase 23% between one and five months post-stroke 24% six months or more post-stroke (Burton et al. 2013)
Emotionalism	20-25% in first six months 10-15% at 12 months (Hackett et al. 2010)
Pain	Up to 42% (van Wijck 2013)
Cognitive problems and dementia	Approximately 66% develop cognitive problems Approximately 33% develop dementia (Melkas et al. 2014)

Financial cost of stroke

The financial cost of stroke is substantial. It has been estimated that the financial burden of stroke on the UK is £8.9 billion a year (Saka, McGuire and Wolfe 2009). This includes the direct costs of stroke such as diagnosis and hosptial care as well as the indirect costs such as lost income due to disability and death, social benefit payments and informal care from professionals, carers and friends and family. The breakdown of the estimate of the cost of stroke (Table 1.5) indicates that the long term costs of stroke such as community care, informal care costs and productivity are much greater than the costs associated with the acute phase such as diagnosis and inpatient care.

Table 1.5 - Financial costs of stroke in the UK per year. (Saka, McGuire and Wolfe 2009, p29).

Cost item	**Cost (in millions of pounds sterling)**
Diagnosis costs	45.604
Inpatient care costs	865.872
Outpatient costs	109.679
Outpatient drug costs	505.588
Community care costs	2,857.113
Annual care cost total	**4,383.858**
Informal care costs total	**2,420.921**
Income lost due to mortality	592.733
Income lost to morbidity	740.158
Productivity loss total	**1,332.892**
Benefit payments	841.254
Total	**8,978.926**

Therefore due to the increase in people surviving for years after stroke, the numerous problems that survivors experience in the subsequent months and years and the human and monetary cost of rehabilitation, it is vital that stroke is considered to be a chronic disease and that research investigates how life can be improved for stroke survivors in the long term.

One of the complications of stroke that has been under researched to date is fatigue. Fatigue is a very important symptom to investigate further. One study of the opinions of stroke survivors, caregivers and health professionals identified it as one of the ten most important research priorities relating to life after stroke (Pollock et al. 2014). Many stroke survivors report it to be their "worst or one of their worst symptoms" (Parks et al. 2012, p621; Ingles, Eskes and Phillips 1999, p175) and yet al.most half of fatigued stroke survivors feel that they had not received enough help for this symptom (McKevitt et al. 2010).

Fortunately some research has already been done about fatigue after stroke and this will be reviewed in the next section.

The Problem of Stroke Summary

- Stroke is the second most common cause of death worldwide.
- Incidence of stroke is declining in the UK but more people are surviving strokes meaning the number of people currently living having had a stroke is increasing.
- These stroke survivors suffer from numerous complications and impairments.
- Therefore stroke should be considered to be a long term chronic disease.
- Fatigue is a post-stroke problem which is currently under-researched.

Section 2 - Review of Fatigue after Stroke Literature

Literature Review Approach

The literature search was conducted in MEDLINE (from 1966), EMBASE (from 1980), CINAHL (from 1937) and PsycInfo (from 1806) originally on 7th April 2011 and then again on 9th January 2015 in MEDLINE, EMBASE and PsycInfo. The keywords "fatigue" and "stroke" and their associated terms or synonyms were used. The same search terms were used in a Cochrane systematic review of interventions for post-stroke fatigue. See Appendix 3 for a full list of search terms used.

Papers were selected for the literature review if they were less than seven years old or if they were a "key" paper (a key paper is one where the main topic of the paper was fatigue after stroke).

Although these databases were systematically searched, this literature review should not be considered to be a "systematic review". Systematic reviews have a specific purpose. They are used to gather and synthesize the best evidence available in order to answer a specific research question (The Campbell Collaboration) whereas this literature review aims to provide an overview of previous research on fatigue after stroke so that the need for the research in subsequent chapters of this thesis can be justified and put into context.

What is Post-Stroke Fatigue (PSF)?

There is no universally accepted definition of post-stroke fatigue in the literature. The most common definition is that it is “a feeling of early exhaustion with weariness, lack of energy and aversion to effort” (Stokes, O'Connell and Murphy 2011, p2; Lewis et al. 2011, p295; Annoni et al. 2008, pS244; Barker-Collo, Feigin and Dudley 2007; Colle et al. 2006, p1; Staub and Bogousslavsky 2001, p75). It has also been defined as “a state of weariness unrelated to previous levels of exertion and is associated with pathological factors” (Tseng et al. 2010, p2908), “a feeling of physical tiredness and lack of energy that is described as pathological, abnormal, excessive, chronic, persistent or problematic” (de Groot, Phillips and Eskes 2003, p1715), “an unpleasant physical cognitive and emotional symptom described as a tiredness not relieved by common strategies that restore energy” (Barker-Collo, Feigin, and Dudley 2007, p1), " a lack of energy or feeling of physical tiredness" (Miller et al. 2013, p347), "the awareness of a decreased capacity for physical or mental activity due to an imbalance in the availability, utilization or restoration of resources needed to perform activity" (Vuletic, Lezaic and Morovic 2011, p341), "the subjective lack of physical or mental energy to carry out usual and desired activities as perceived by the patient" (Tang et al. 2013, p131) and "a lack of energy in physical, social or cognitive tasks" (Parks et al. 2012, p620).

One group of researchers attempted to resolve the problem that there is presently no valid, reliable and universally accepted definition of post-stroke fatigue by developing a case definition for clinically significant fatigue (Lynch et al. 2007).

They defined clinically significant fatigue as a feeling of lack of energy which can be distinguished from a feeling of sleepiness or lack of motivation. The patient must have experienced this feeling for more than 50% of the day, every day or nearly every day during the past month and this fatigue must have been a problem for the patient by interfering with everyday activities.

The nature of post-stroke fatigue can be distinguished from fatigue which is caused by exercising. Post-stroke fatigue is considered to be a chronic, subjective experience which is often out of proportion to the amount of previous activity (Staub and Bogousslavsky 2001) and is often not resolved by sleep or rest (McGeough et al. 2009). Exercise-related fatigue is a more objective fatigue. It is a physiological response to overexertion, is acute in nature and can be ameliorated by rest (Tseng et al. 2010; McGeough et al. 2009).

Impact of fatigue after stroke

Fatigue has a significant detrimental impact on many aspects of a stroke survivor's life. Fatigued stroke survivors are less likely to return to paid work (Andersen et al. 2012), full time employment (Roding et al. 2003) or driving (Perrier, Korner-Bitensky and Mayo 2010) after their stroke. They are more likely to become dependent on others for daily activities such as housework or shopping (Glader, Stegmayr and Asplund 2002; van der Werf et al. 2001; Sisson 1998) and are significantly more likely to have lower scores on measures of health related quality of life (Naess et al. 2012a; Parks et al. 2012; Tang et al. 2010b; Visser-Meily et al. 2008; Naess et al. 2006). Fatigue has also been reported to have a detrimental effect on the social and family lives of stroke survivors. Specifically female participants in one study indicated that fatigue made it harder for them to properly care for their children (Roding et al. 2003) and in another study stroke survivors reported that fatigue was to blame for the loss of friendships due to them being too tired to socialise (Northcott and Hilari 2011).

Fatigue can also adversely affect patients' participation in the rehabilitation process (de Groot, Phillips and Eskes 2003; Michael 2002; Ingles, Eskes and Philliips 1999) and hinder patients' physiotherapy sessions (Morley, Jackson and Mead 2005). One prospective study reported that those who had fatigue at one year after stroke were more at risk of a reduction in mobility between one and three years after stroke onset (van de Port et al. 2006).

It has also been reported that 40% of stroke survivors said "that fatigue was either their worst symptom or one of their worst symptoms" and 27% reported having fatigue problems on a daily basis (Ingles, Eskes and Phillips 1999, p175). In addition to this, a study reported that 43% of fatigued stroke survivors felt they had not been given enough help for fatigue since their stroke (McKevitt et al. 2010). Another study reported that 41% agreed that fatigue was one of their three most troublesome symptoms (Naess et al. 2012) and another study reported that out of those stroke survivors who experienced fatigue, 59.5% said it was the "worst or one of the worst symptoms" (Parks et al. 2012, p621).

Finally one study found that stroke survivors who indicated they were "always tired" two years after stroke were significantly more likely to have died one year later (at three years after stroke onset) even after depression, age, gender, activities of daily living functions and marital status had been accounted for (Glader, Stegmayr and Asplund 2002, p1330). Another study reported that more fatigue was associated with shorter survival even when pain, social role functioning, physical function and general health were taken into account (Mead et al. 2011) and a third study reported that fatigue was an independent predictor of mortality even when presence of diabetes and history of myocardial infarction were taken into account (Naess et al. 2012).

Frequency of fatigue

The details of studies which reported the frequency of fatigue at one time point after stroke are presented in Table 1.6. Studies which reported the frequency of fatigue at more than one time point will be discussed in detail in Chapter 2.

The literature suggests that fatigue is a common symptom after stroke but there is little consensus regarding exactly how common it is. Table 1.6 shows that the proportion of stroke survivors with fatigue after stroke ranges from 16% (Hubacher et al. 2012) to 86% (Palmcrantz, Holmqvist and Sommerfeld 2012). The median frequency of fatigue of all the studies mentioned in Table 1.6 is 49% and the IQR is 39.5-59.5%. This difference in frequency estimates is probably due to the large amount of heterogeneity between studies. For instance, the time after stroke that fatigue was assessed at ranged from 23 days (Lynch et al. 2007) to a mean of 85 months (Robinson et al. 2011), the mean or median age of participants ranged from 47.8 (Naess et al. 2005; Naess et al. 2006) to 78 years (Morley, Jackson and Mead 2005), and a variety of instruments for assessing fatigue were used across all the studies. These instruments will be discussed in more detail in the next section.

Table 1.6 - Details of studies which reported the frequency of fatigue at one time point

Study	N	Type of stroke	Age (years)	Gender	Method of assessing fatigue	Time after stroke	Percentage reporting fatigue
Andersen et al. 2012	83	First ever ischaemic and haemorrhagic Excluded SAH	53.8 (45.4-58.2)	52% Male	Multidimentional Fatigue Inventory-20 (MFI-20) Cut-off score ≥ 12	2 years	57%
Appelros 2006	253	First ever ischaemic and haemorrhagic Excluded SAH	74.5 Median 76 Range 33-95	49% Male	Semi-structured interview	1 year	53%
Carlsson, Moller and Blomstrand 2003	75	First ever ischaemic and haemorrhagic Excluded SAH	75 or less 59.6 (11.3)	69% Male	Semi-structured interview to assess mental fatigability	1 year	72%
Choi-Kwon et al. 2005	220	First ever ischaemic and haemorrhagic	60	72.7% Male	Visual analogue scale Fatigue Severity Scale Fatigue Impact Scale	3-27 months (mean 15 months)	57%
Crosby et al. 2012	64	Ischaemic 56% Haemorrhage 20% Missing 24%	73.5 (14.0)	33% Male	Fatigue Severity Scale Cut off score ≥ 44 Question "Do you consider that fatigue is a problem for you?"	4.9 months (4.6)	48% scored 44 or more on FSS 64% answered yes indicating that fatigue was a problem for them.

Feigin et al. 2012	613	First and recurrent ischaemic stroke	67.0 (12.9) in men 73.2 (12.2) in women	53.8% Male	SF-36 Vitality Score A score of one SD below the New Zealand norm mean indicated fatigue.	6 months	29.9%
Glader, Stegmayr and Asplund 2002	3667	Did not specify whether first or recurrent ischaemic and haemorrhagic Excluded SAH	71.8	53.8% Male	Single questions "Do you feel tired" Four possible answers: never, sometimes, often or always.	Mean 30.4 months (SD 1.7)	39%
Hoang et al. 2012	32	First or recurrent ischemic 66%	64.6 (11.2)	66% Male	Fatigue Severity Scale Cut off score ≥ 4	40 months (42.2)	66%
Hubacher et al. 2012	31	First or recurrent ischaemic 90% ICH 10%	59.3 (10.3)	81% Male	Fatigue Severity Scale Cut off score ≥ 4.6 Modified Fatigue Impact Scale Fatigue Scale for Motor and Cognitive Functions	50.65 days (31.57)	FSS 16.1% MFIS 35.5% FSMC 58.1%
Huijts et al. 2012	40	Ischaemic lacunar stroke	67.9 (12.6)	62% Male	Checklist Individual Strength Cut off score Above 76	3 months	42.5%
Ingles, Eskes and	88	Did not specify	66.6 (13.4)	62.5% Male	Fatigue Impact Scale – modified version	3-13 months	68%

Phillips 1999		whether first or recurrent ischaemic and haemorrhagic Excluded SAH					
Jaracz, Mielcarek and Kozubski 2007	50	First ever ischaemic and haemorrhagic	55 (7.8)	66% Male	Polish version of Fatigue Impact Scale	3 months	30%
Lerdal et al. 2011	115	First ever	68.3 (13.3)	59%	Fatigue Severity Scale FSS < 4 - No or low fatigue FSS 4-4.9 - Moderate fatigue FSS 5 or above - Severe fatigue	First two weeks following a stroke	No or low fatigue - 43% Moderate fatigue - 33% Severe fatigue - 24%
Lynch et al. 2007	55	First or recurrent ischaemic and haemorrhagic	73 (66-81)	56% Male	Fatigue Case Definition for clinically significant fatigue	Mean of 23 days for inpatients Mean of137 days for community patients	36.4%
McKechnie, Lewis and Mead 2010	28	First or recurrent ischaemic and haemorrhagic	Mean 73	46.4% Male	Fatigue Case Definition for clinically significant fatigue	35 days 3-89 days	53%

Michael, Allen and Macko 2006	53	Did not specify whether first or recurrent	Mean 66 Range 45-84	58.5% Male	Fatigue Severity Scale Cut-off score ≥ 4	6-166 months (mean 10.3)	46%
Michael and Macko 2007	79	Did not specify whether first or recurrent	Mean 65 Range 45-84	53% Male	Fatigue Severity Scale Cut-off score ≥ 4	6-120 months (mean 10)	42%
Miller et al. 2013	77	Ischaemic 44.2% Did not specify whether first or recurrent	Mean 64.1 Range (48-89)	75.3% Male	Fatigue Severity Scale Cut off Score > 4	79.2% were over 1 year since stroke 20.8% were between 6 months and 1 year since stroke	66%
Morley, Jackson and Mead 2005	20	Not reported	Median 78	Not reported	Fatigue Severity Scale Cut-off score ≥ 5	Median 62.5 days	40%
Naess et al. 2005	192	First ever infarction Haemorrhagic excluded SAH excluded	47.8	57.3% Male	Fatigue Severity Scale Cut off score ≥ 4	6 years 1.4-12.3 years	51.3%
Naess et al. 2006	190	First ever infarction Haemorrhagic excluded	47.8	57% Male	Fatigue Severity Scale Cut off score ≥ 4	6 years 1.4-12.3 years	52%

		SAH excluded					
Naess et al. 2012b	328	First or recurrent cerebral infarction	67.7	63% Male	Fatigue Severity Scale Cut off score ≥ 5	372 days Range 185-757 days	46%
Palmcrantz, Holmqvist and Sommerfeld 2012	158	Ischaemic 80% ICH 18% Not specified 2%	Median 59 IQR 54-62	66% Male	The Map Young Persons with Stroke (MYS) questionnaire	15% <1 year 20% >1 year 14% >2 years	86% reported experiencing tiredness sometimes, frequently or constantly.
Park et al. 2009	40	First ever	59.9 (11.8)	65% Male	Fatigue Severity Scale Cut off score ≥ 4	32.7 months (27.4)	30%
Passier et al. 2011a	108	SAH	53.4 (12.3)	17.6% Male	Fatigue Severity Scale Cut off score ≥ 4	1 year	71%
Robinson et al. 2011	50	First ever Did not specify type	65 (8.4)	54% Male	Fatigue Severity Scale Cut off score ≥ 36	85 months (6 to 358 months)	48%
Rothwell et al. 2013	137	Excluded SAH	Mean 72.6 Range 40-93	55.5% Male	GM-SAT Asked if fatigue was a problem that was being addresssed	6 months post hospital discharge	34.3%
Smith et al. 2008	80	Did not specify whether first or recurrent,	74.1 (6.6)	55% Male	Fatigue Assessment Scale Cut off score ≥ 13	7.6 months (5.4)	61.3%

		ischaemic or haemorrhagic were included					
Stokes, O'Connell and Murphy 2011	100	First ever ischaemic or haemorrhagic	72.4 (9)	55% Male	Multidimensional Fatigue Inventory – 20 Cut off score ≥ 12	16 months (1-36 months)	General 58% Physical 85% Activity related 75% Motivational 48% Mental 69%
Tang et al. 2010a	334	First or recurrent ischaemic Haemorrhagic excluded	With fatigue 65 (11.3) Without fatigue 66.4 (11.8)	65% Male	Fatigue Severity Scale Cut-off score ≥ 4	3 months	23%
Tang et al. 2014	199	First or recurrent ischaemic Stroke	Fatigued group 66.0 (10.1) Not fatigued group 69.1 (10.0)	Fatigued group 66% Male Not fatigued group 71.7% Male	Chinese version of Fatigue Severity Scale Cut off score ≥ 4	3 months	23.6%
Valko et al. 2008	235	Did not specify	63 (14)	69% Male	Fatigue Severity Scale Cut-off score	1.21 years (0.62)	49%

		whether first or recurrent ischaemic Haemorrhagic excluded			≥ 4		
Van de Port et al. 2007b	165	First ever ischaemic, haemorrhagic and SAH were included	57 (11)	55% Male	Fatigue Severity Scale Cut-off score ≥ 4	1 year	68%
Van de Port, Kwakkel and Linderman 2008	72	First ever ischaemic, haemorrhagic and SAH were included	59 (10)	64% Male	Fatigue Severity Scale Cut-off score ≥ 4	3 years	46%
Van der Werf et al. 2001	90	First or recurrent ischaemic or haemorrhagic	62.1 Range (32-73)	72% Male	Checklist Individual Strength Cut off score ≥ 40 Asked whether fatigue was main complaint	3.8 years	51% above CIS cut-off 50% reported fatigue was main complaint/
Visser-Meily et al. 2008	141	SAH	51.4 (12.3)	33.3% Male	Fatigue Severity Scale Cut-off score ≥ 4	36.1 months (23-52)	67%
Vuletic, Lezaic and Marovic 2011	35	First ever stroke	61.8 (14.2)	Not specified	Fatigue Severity Scale Cut off score > 4	3 months	45%
Winward et	73	First or	Median	58%	Chalder Fatigue Scale	6 months	56%

al. 2009		recurrent ischaemic or haemorrhagic	74.1 (IQR 64.5-80)	Male	Cut-off score > 3		

Frequency of fatigue in healthy controls compared to stroke survivors

Six of the studies that reported the frequency of fatigue after stroke also recruited a control group so the frequency of fatigue in healthy people of a similar age could be directly compared. (Table 1.7) These six studies (Vuletic, Lezaic and Morovic 2011; Stokes, O'Connell and Murphy 2011; Valko et al. 2008; Naess et al. 2005; van der Werf et al. 2001; Ingles, Eskes and Phillips 1999) reported the frequency of fatigue in age-matched healthy controls to range from 7% to 36% and the frequency of fatigue in stroke survivors to range from 45% to 85%. Calculated odds ratios for these six studies ranged from 2.2 to 32.1 meaning that the odds of a stroke survivor being fatigued are much greater than the odds of a member of the general population being fatigued (Table 1.7).

Table 1.7 – Frequency of fatigue after stroke compared with the frequency of fatigue in age matched healthy controls.

Study	**Method of assessing fatigue (cut-off)**	**Stroke patients**	**Healthy controls**	**Odds ratios with 95% CI**
Ingles, Eskes and Phillips 1999	Fatigue Impact Scale	F = 60 (68%) NF = 28 (32%)	F = 20 (36%) NF = 36 (64%)	3.9 1.9-7.8
Naess et al. 2005	FSS ≥ 4	F = 98 (51%) NF = 94 (49%)	F = 18 (32%) NF = 38 (68%)	2.2 1.2-4.1
Stokes, O'Connell and Murphy 2011	Multidimensional Fatigue Inventory - 20 ≥ 12			
-General		F = 58 (58%) NF = 42 (42%)	F = 11 (11%) NF = 89 (89%)	11.2 5.3-23.5
-Physical		F = 85 (85%) NF = 15 (15%)	F = 15 (15%) NF = 85 (85%)	32.1 14.8-69.8
-Activity		F = 75 (75%) NF = 25 (25%)	F = 18 (18%) NF = 82 (82%)	13.7 6.9-27.0
-Motivational		F = 48 (48%) NF = 52 (52%)	F = 7 (7%) NF = 93 (93%)	12.3 5.2-29.1
-Mental		F = 69 (69%) NF = 31 (31%)	F = 9 (9%) NF = 91 (91%)	22.5 10.1-50.4
Valko et al. 2008	FSS ≥ 4	F = 115 (49%) NF = 120 (51%)	F= 82 (18%) NF = 372 (82%)	4.3 3.1-6.2
Van der Werf et al. 2001	Checklist Individual Strength ≥ 40	F = 46 (51%) NF = 44 (49%)	F = 6 (12%) NF = 44 (88%)	7.7 3.0-19.8
Vuletic, Lezaic and Morovic 2011	FSS > 4	F = 16 (45%) NF = 19 (55%)	F = 4 (11%) NF = 31 (89%)	6.5 1.9-22.5

F = fatigued
NF = Not fatigued

How is fatigue assessed or measured?

In the literature fatigue after stroke has been assessed by three categories of self-report method: multi-item scales, single item scales and semi-structured interviews.

Multi-item Scales

A number of multi-item scales have been used to assess fatigue after stroke and there are variations regarding exactly what each scale measures. For instance some scales focus on the physical aspects of fatigue, some focus on more mental of psychosocial aspects of fatigue and some focus on how fatigue impacts on daily life. The characteristics of each scale are described in Table 1.8.

Table 1.8 Multi-item scales which have been used in fatigue after stroke research.

Name of multi-item scale	Further Information
Fatigue Severity Scale (FSS) (Krupp et al. 1989)	• Most commonly used scale in the stroke literature. • Scale consists of nine items. Participant responds to each item on a seven point scale • The content of this scale concentrates on how fatigue impacts on daily life.
Checklist Individual Strength (CIS) subjective fatigue subscale. (van der Werf 2001)	• Scale consists of eight items that the participant responds to on a seven point scale. • It focuses on the more physical aspects of fatigue.
Fatigue Impact Scale (FIS) (Fisk et al. 1994)	• Questionnaire consists of 40 questions: ten questions refer to cognitive fatigue, ten to physical fatigue and 20 questions regard social functioning • Concentrates more on the psychosocial aspects of fatigue.

Modified Fatigue Impact Scale (MFIS) (Larson 2013)	• Questionnaire also assesses fatigue in relation to cognitive, physical and social functioning but only consists of 21 items.
Fatigue Assessment Scale (FAS) (Michielson, De Vries and van Heckguus 2001)	• Questionnaire consists of ten items that participant responds to on a five point scale. • It assess both the physical and mental aspects of fatigue.
Multidimensional Fatigue Inventory (MFI-20) (Smets et al. 1995)	• Questionnaire consists of 20 items that can be split into five separate dimensions. • These dimensions are general fatigue, physical fatigue, activity-related fatigue, motivational fatigue and mental fatigue.
Chalder Fatigue Scale (CFS) (Chalder et al. 1993)	• Questionnaire consists of 14 items which can be split into two dimensions: physical fatigue and mental fatigue.
Multidimensional Fatigue Symptom Inventory - Short Form (MFSI-SF) (Stein et al. 2004)	• Questionnaire consists of 30 items which are split into five separate subscales. • These subscales are general fatigue, emotional fatigue, mental fatigue, physical fatigue and vigour.
Profile of Mood States (POMS) fatigue subscale (McNair, Lorr and Droppelman 1981)	• Questionnaire consists of seven items which measure global fatigue severity.
MOS 36-item Short Form Health Survey (SF-36) vitality subscale (Ware and Sherbourne 1992)	• Consists of four items and assesses vitality, energy levels and fatigue.
The Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al. 2009)	• Questionnaire consists of 20 items. A cognitive and a physical subscale consisting of 10 items each.
The Nottingham Health Profile (NHP) energy dimension (Hunt et al. 1981)	• Scale consists of three statements which respondents answer either yes or no to.
The Neurological Fatigue Index for Stroke (NFI-Stroke) (Mills et al. 2012)	• Questionnaire consists of physical, cognitive and summary subscales.
Fatigue Assessment Instrument (FAI) (Schwartz, Jandorf and Krupp 1993)	• Questionnaire consists of 29 items • It aims to determine the severity, pervasiveness and consequences

	of fatigue and how it responds to sleep

Cut-off scores for fatigue on multi-item scales

Most of the studies mentioned in Table 1.6 which used a multi-item scale specified a cut-off score for fatigue. However only three studies revealed their rationale for deciding on a particular cut-off score. Two studies (Park et al. 2009; Naess et al. 2005) stated that they had used a cut-off score of 4 as a previous study of MS patients had found that 5% of healthy controls scored 4 or above on the Fatigue Severity Scale. The third study (Smith et al. 2008) used a cut-off score of 13 on the Fatigue Assessment Scale as the highest 20% of healthy controls in their study scored 13 or above.

If one study is defining problematic fatigue as a severity level that 5% of the general population experience and another study is defining problematic fatigue as a severity level that 20% of the general population experience then meaningful comparisons cannot be made between different studies regarding the frequency of fatigue. This suggests there is a need for the method of determining a cut-off score to be standardised across all fatigue scales.

It should also be taken into consideration that using cut-off scores to determine the presence or absence of fatigue may be problematic as this method of analysing data does not tell the whole story. For instance, one patient may have scored very highly on a multi-item scale and have a very severe fatigue which profoundly affects many aspects of their life, whereas another patient may have scored just above the cut-off and although this patient is fatigued , they may feel their fatigue is not too much of a problem for them, yet both these patients would be labelled the same or put in the same analysis category. Therefore using cut-off scores to analyse data may over-simplify the data which can result in losing information.

Psychometric properties of multi-item scales

The psychometric properties of these multi-item scales have mostly been tested in the general population and in other patient groups rather than in stroke patients. It is important that these multi-item scales are tested for reliability and validity in stroke patients as the nature of fatigue may differ greatly in different diseases and a scale which is valid and reliable in one patient group may not be in another group. The reliability of a scale refers to its ability to produce consistent, reproducible results and the validity of a scale refers to its ability to measure what it is intended to measure (Field 2005).

Only four studies have evaluated the validity and reliability of multi-item fatigue scales in stroke survivors. One study compared the validity and reliability of four different fatigue scales (Mead et al. 2007). These researchers recommended the Fatigue Assessment Scale as even though they reported that it did not have high internal consistency, it was found to have high construct validity and the best test-retest reliability compared to other scales (MFSI, SF-36 vitality subscale, POMS fatigue subscale fatigue). These results were supported by another study (Smith et al. 2008) which evaluated the FAS in 80 stroke patients. This study also reported the

FAS to have good reliability and validity but unlike Mead et al. (2007), they found it to have good internal consistency as well.

The reliability and validity of the FAS will be discussed further in Chapter 4.

A recent study (Lerdal and Kottorp 2011) examined the psychometric properties of the FSS in people with stroke. They tested the FSS for uni-dimensionality, various types of validity and the FSS's reliability and precision. Their main conclusion was that the validity and reliability of the FSS could be improved if the first two items on the scale are removed and only the remaining seven items are used when assessing fatigue in a stroke population. They recommend that this shorter version should be used in future research.

Valko et al. (2008) also investigated the psychometric properties of the FSS in stroke patients as well as in patients with MS, sleeping disorders and in healthy subjects. They reported the FSS to have excellent internal consistency and to have high test-retest reliability. This study reported that items 1 and 2 on the FSS had the lowest internal consistency, but they did not recommend that these items be dropped from the scale.

Single Question method of assessing fatigue

Some studies used only a single question or a single item on a larger scale to assess fatigue in stroke survivors. For instance one study asked patients the question "Do you feel tired" to which they responded with one of 4 possible answers; never, sometimes, often, always (Glader, Stegmayr and Asplund 2002). Another study used the Map Young Persons with Stroke (MYS) questionnaire which has a single question relating to tiredness to which participants can answer "constantly", "frequently", "sometimes" or "almost never" (Palmcrantz et al. 2012).

Semi-structured interviews

Semi-structured interviews have also been used as a method of investigating stroke patient's experiences of fatigue. For instance, one study used semi-structured interviews to ascertain how many stroke survivors had a problem with mental fatigability (Carlsson, Moller and Blomstand 2003) and another study used semi-structured interviews to investigate participants' general experiences of fatigue (Appelros 2006).

Case Definition for fatigue after stroke

Fatigue after stroke has also been assessed by a case definition with an associated structured interview (McKechnie, Lewis and Mead 2010; Lynch et al. 2007). The details of this interview (including its validity and reliability) will be described in detail in Chapter 4.

Qualitative Studies

Fatigue after stroke has also been investigated by asking stroke survivors to describe their subjective experiences of fatigue through semi-structured interviews and then analysing their responses by using a variety of qualitative methodologies.

A systematic review identified and synthesized 12 qualitative studies of stroke survivors' experiences of post-stroke fatigue (Eilertsen, Ormstad & Kirkevold 2013). Across all 12 of these studies five "core characteristics" (p518) of the experience of post-stroke fatigue could be identified. Those with fatigue described that: 1) they did not have enough energy to carry out everyday tasks or activities 2) they had a requirement to sleep which was not normal 3) they were very easily tired out by activities and needed to rest more often than normal 4) they were unable to predict when or in what situations their fatigue would appear and 5) they were more inclined to be affected by stress. This review also reported that a common theme was that fatigue was often not acknowledged by stroke survivors' friends, family and health care workers and this lack of acknowledgement caused great distress and negatively affected the strategies stroke survivors used to cope with their fatigue. The review also suggested three main categories of how stroke survivors cope with fatigued. Some stroke survivors reported that they were "struggling to cope" (p520). They felt guilty about sleeping during the day, found fatigue to be very frustrating and spent a lot of mental energy trying to find validation for their fatigue and coping strategies which were acceptable to their friends and family. Other stroke survivors reported that they coped by "taking the fatigue into account" (p521) when deciding which activities to take part in or the length of time they would dedicate to the activity. Finally, some stroke survivors would cope by "trying to win over" (p521) the fatigue. They described that they perceived fatigue as a challenge and were determined to find ways to overcome their fatigue and return to normal energy levels.

Factors associated with fatigue after stroke

Many research studies (cross-sectional and longitudinal) have investigated which patient characteristics may be associated with fatigue after stroke.

Gender

A small number of studies have found an association between gender and fatigue after stroke. Five studies reported that women were significantly more likely to be fatigued (Tang et al. 2013; Crosby et al. 2012; Naess et al. 2012; Tang et al. 2010a; Lynch et al. 2007) and three studies reported that, after stroke, women were significantly more likely to obtain higher fatigue scores than men (Perrier, Korner-Bitensky and Mayo 2010; Christensen et al. 2008; Schepers et al. 2006). However the majority of studies that have investigated the relationship between gender and fatigue have found no statistically significant association. (Tang et al. 2014; Lerdal and Gay 2013; Feigin et al. 2012; Parks et al. 2012; Hoang et al. 2012; Vuletic, Lezaic and Morovic 2011; Ormstad et al. 2011; Passier et al. 2011a; Chestnut 2011; Stokes, O'Connell and Murphy 2011; Lerdal et al. 2011; Harbison, Walsh and Kenny 2009; Jaracz, Mielcarek and Kozubski 2007; Appelros 2006; Choi-Kwon et al. 2005; Naess et al. 2005; Staub & Bogousslavsky 2001; van der Werf et al. 2001; Ingles, Eskes and Phillips 1999).

Although it should be pointed out that just because the majority of studies found no statistically significant association with gender does not necessarily mean that no such association exists. These non-significant associations may have occurred because the magnitude of variation in some of the dependent or independent variables in these studies may have been small or some of these studies may not have had sufficient statistical power to detect an effect. This situation may also be true for the variables which will be discussed below.

Age

The majority of studies which have investigated the relationship between fatigue after stroke and the patient's age have found no significant association (Lerdal and Gay 2013; Tang et al. 2013; Hoang et al. 2012; Vuletic, Lezaic and Morovic 2012; Crosby et al. 2012; Stokes, O'Connell and Murphy 2011; Ormstad et al. 2011; Passier et al. 2011a; Lerdal et al. 2011; Tang et al. 2010a; Harbison, Walsh and Kenny 2009; Christensen et al. 2008; Lynch et al. 2007; Appelros 2006; Choi-Kwon et al. 2005; Naess et al. 2005; van der Werf et al. 2001; Ingles, Eskes and Phillips 1999). However seven studies (Naess et al. 2012; Feigin et al. 2012; Mead et al. 2011; Chestnut 2011; Jaracz, Mielcarek and Kozubski 2007; Schepers et al. 2006; Glader, Stegmayr and Asplund 2002) reported that older age was significantly associated with fatigue and conversely two studies reported greater fatigue to be significantly associated with younger age (Parks et al. 2012; Snaphaan, van de Werf and de Leeuw 2011).

Depression

Numerous studies have reported a statistically significant association between measures of depression and measures of fatigue after stroke (Lerdal and Gay 2013; Naess et al. 2012; Feigin et al. 2012; Hubacher et al. 2012; Crosby et al. 2012; Radman et al. 2012; Stokes, O'Connell and Murphy 2011; Snaphaan, van de Werf and de Leeuw 2011; Vuletic, Lezaic and Morovic 2011; Lerdal et al. 2011; Tseng, Gajewski and Kluding 2010; Tang et al. 2010a; Park et al. 2009; Harbison, Walsh and Kenny 2009; Jaracz, Mielcarek and Kozubski 2007; van de Port et al. 2007a; van de Port et al. 2007b; Appelros 2006; Schepers et al. 2006; Naess et al. 2005; Choi-Kwon et al. 2005; Glader, Stegmayr and Asplund 2002; van der Werf et al. 2001). In fact, only one study which was found for this literature review, investigated the relationship between depression and post-stroke fatigue and reported there to be no significant association (Hoang et al. 2012).

This association between mood and fatigue has led to the suggestion that fatigue may be a symptom of post-stroke depression. (Staub and Bogousslavsky 2001). However the evidence for this suggestion is far from conclusive as many of these studies have also demonstrated that fatigue can exist independently of post-stroke depression. For instance one study reported that a larger number of patients experienced fatigue without depression (39%) than experienced both symptoms (29%) (Ingles, Eskes and Phillips 1999). Five studies excluded depressed patients from their analysis and found that 37.1% (Naess et al. 2005), 50% (Choi-Kwon et al. 2005), 57% (Crosby et al. 2012), 37.4% (Naess et al. 2012) and 30% (Vuletic, Lezaic and Morovic 2011) of these non-depressed patients still reported fatigue. One study reported that over half of their participants with either fatigue or depression only suffered severely from one symptom and not both (Harbison, Walsh and Kenny 2009). Another study reported that of those with severe fatigue, only 38% were depressed as well (van der Werf et al. 2001). Finally, Huijts et al. (2012) reported that 42.5% of stroke survivors had severe fatigue but only 15% of patients had clinically significant depression.

A recent systematic review and meta-analysis of psychological associates of post-stroke fatigue reported a statistically significant association between post-stroke fatigue and depressive symptoms (Wu et al. 2014). This association was still present even when patients with clinical depression were excluded from the analysis and when the analysis was limited to depression scales that did not have an item relating to fatigue.

Anxiety

The association between measures of anxiety and measures of post-stroke fatigue has been reported in the literature substantially less often than the relationship between depression and fatigue. Six studies have reported that higher anxiety levels were significantly associated with more fatigue (Radman et al. 2012; Vuletic, Lezaic and Morovic 2011; Snaphaan, van der Werf and de Leeuw 2011; Harbison, Walsh and Kenny 2009; Lynch et al. 2007; Glader, Stegmayr and Asplund 2002) and one has reported an association between post-stroke fatigue and anxiety which was not statistically significant (Zedlitz, Fasotti and Geurts 2011). The meta-analysis carried out by Wu et al. (2014) was able to include four of these seven studies and reported "a trend towards an association" (p1781) but this was not statistically significant.

In addition to these seven studies, it has also been reported that patients with post-traumatic stress disorder (PTSD) were significantly more fatigued than those without PTSD at both three and 13 months post-stroke (Noble 2008).

It has also been demonstrated that although anxiety is associated with fatigue it can also exist separately with one study reporting that fatigue was present in 42.3% of patients who did not experience significant anxiety (Naess et al. 2005).

Sleep Disorders

Sleep disorders such as insomnia or sleep apnea are more common after stroke (Colle et al. 2006; Staub and Bogousslavsky 2001) and may partly explain or influence the development of fatigue. Three studies asked patients if they were experiencing any insomnia or frequent awakening during the night and found there to be a significant relationship between fatigue and these sleep disturbances (Naess et al. 2012; Park et al. 2009; Appelros 2006). Another study found fatigue to be associated with the presence of insomnia but only before depression had been controlled for (Choi-Kwon et al. 2005) and another study reported a significant association between fatigue and poorer sleep quality (Lerdal et al. 2011). Two studies did not find any association between fatigue and sleeping problems (Schepers et al. 2006, Hoang et al. 2012) and one study reported there was no association between sleeping disorders in the month before stroke onset and fatigue after stroke (Feigin et al. 2012).

Disability

A number of studies have investigated whether disability may be associated with fatigue after stroke. The instruments used to assess disability include the Modified Rankin Scale (van Swieten et al. 1988), the Barthel Index (Granger et al. 1979), the Oxford Handicap Scale (Bamford et al. 1989) and the Glasgow Outcome Scale (Jennett and Bond 1975). Several of these studies have reported that higher levels of fatigue are significantly related to greater physical impairment, disability or dependency on others for activities of daily living (Tang et al. 2013; Feigin et al. 2012; Vuletic, Lezaic and Morovic 2011; Ormstad et al. 2011; Passier et al. 2011a; Lerdal et al. 2011; Christensen et al. 2008; Jaracz, Mielcarek and Kozubski 2007; Appelros 2006; Naess et al. 2005; Choi-Kwon et al. 2005; Glader, Stegmayr and Asplund 2002; van der Werf et al. 2001). However almost as many studies did not find a significant association between fatigue and disability (Tang et al. 2014; Hoang et al. 2012; Parks et al. 2012; Crosby et al. 2012; Stokes, O'Connell and Murphy 2011; Tang et al. 2010a; Park et al. 2009; Smith et al. 2008; van de Port et al. 2007a; Naess et al. 2006; Ingles, Eskes and Phillips 1999). One study reported a significant association between fatigue and disability at baseline but that this association was no longer significant at 18 months post-stroke (Snaphaan, van de Werf and de Leeuw 2010).

Interestingly one study reported that higher levels of disability *before* stroke onset were a predictor of cognitive, psychosocial and physical fatigue after stroke onset (Parks et al. 2012).

Stroke Severity

It has also been investigated whether there is an association between fatigue and stroke severity as measured by either the NIHSS or the Scandinavian Stroke Scale. One study reported that fatigue was more prevalent in patients with higher stroke severity scores but they also reported that those who scored zero on the NIHSS in the days immediately after stroke onset were still more likely to be fatigued at six months than patients who were diagnosed with a TIA (Winward et al. 2009). Another study found an association between fatigue and stroke severity but did not report the direction of the association (Appelros 2006) and a third study reported that *higher* stroke severity scores were significantly associated with *lower* fatigue scores (Jaracz, Mielcarek and Kozubski 2007).

However six studies did not find a significant association between fatigue and stroke severity (Tang et al. 2013; Parks et al. 2012; Snaphaan, van de Werf and de Leeuw 2011; Tang et al. 2010a; Christensen et al. 2008; Ingles, Eskes and Phillips 1999).

Previous Stroke

Two studies reported previous stroke to be significantly associated with fatigue (Glader, Stegmayr and Asplund 2002; Parks et al. 2012), however one study reported that patients who had had a previous stroke were significantly less likely to be fatigued (Feigin et al. 2012) and another four studies reported that they found no significant association between previous stroke and fatigue (Tang et al. 2014; Tang et al. 2013; Crosby et al. 2012; Snaphaan, van der Werf and de Leeuw 2011).

Pre-stroke fatigue

Only two studies have examined the relationship between fatigue after stroke and fatigue before stroke onset (Lerdal et al. 2011; Choi-Kwon et al. 2005). They both reported that pre-stroke fatigue to be significantly associated with fatigue after stroke. This could be interpreted as evidence that fatigue after stroke is not connected to the stroke itself but is instead a continuation of a symptom which the patient previously suffered from. However one of these studies (Choi-Kwon et al. 2005) reported that 36% of stroke patients that did not have a fatigue problem before their stroke went on to develop fatigue after their stroke indicating that fatigue after stroke can exist independently of fatigue before stroke.

In addition, stroke survivors have reported that fatigue after stroke is qualitatively different from fatigue they experienced before their stroke (Radman et al. 2012; Roding et al. 2003).

Pain

It has also been investigated whether stroke survivors who are in pain are more likely to be fatigued. Four studies reported that greater amounts of pain are significantly associated with higher fatigue levels (Hoang et al. 2012; Naess et al. 2012b; Naess et al. 2007; Glader, Stegmayr and Asplund 2002) whereas another two studies found no significant relationship between these two symptoms (Miller et al. 2013; Appelros 2006,).

Psychosocial factors

Higher levels of fatigue have been reported in patients who believed they had not completely recovered compared to those who believed they had completely recovered (Winward et al. 2009). Fatigue has also been found to be associated with a patient's locus of control. In other words, higher levels of fatigue are reported in patients who believe health care professionals or carers are in control of their recovery rather than believing that they have control over their own recovery (Schepers et al. 2006). One study examined fatigue in relation to a patient's style of coping in stressful situations and found it was significantly associated with task orientated, emotion orientated and avoidance orientated style of coping (Jaracz, Mielcarek and Kozubski 2007). One study found a significant association between higher levels of fatigue and how confident stroke survivors felt about their ability to manage their own stroke symptoms (chronic disease self-efficacy) and their confidence in their ability to balance in a variety of situations (balance self-efficacy) (Miller et al. 2013). Three studies reported that worse emotional role function and worse mental health as assessed by the SF-36 was significantly associated with higher levels of fatigue (Mead et al. 2011; Lewis et al. 2011; Tang 2010b).

However one study investigated the relationship between fatigue and a variety of psychosocial characteristics including psychological distress, coping styles, social support and self-efficacy. They reported a significant relationship between fatigue and the obsessive-compulsive, somatic complaints and depression subscales of the psychological distress symptoms checklist but found no other significant associations between fatigue and the other psychosocial characteristics (Zedlitz et al. 2011).

Biological correlates of fatigue

A recent systematic review examined whether fatigue after stroke may have a biological basis (Kutlubaev, Duncan and Mead 2012). This review searched for studies that had investigated associations between fatigue and stroke lesion location, pathological type of stroke, white matter lesions, brain atrophy and inflammation.

The review reported that most studies (9 out of 11) that investigated the relationship between fatigue and side of lesion found no association and that most studies (7 out of 12) that examined the relationship between site of lesion and fatigue also found no association. There was no consensus among the remaining five studies regarding which site of lesion was related to fatigue. One study did report that fatigue was worse in ischaemic stroke patients than those who had an intracerebral haemorrhage, however another five studies failed to find an association between fatigue and pathological type of stroke. The review reported that only one study had investigated the association between fatigue and white matter lesions and brain atrophy and that this study did not find a relationship between fatigue and these factors. Finally one study reported that even after mood and pre-stroke fatigue were taken into account, patients with higher CRP levels were more likely to be fatigued.

Since that review was carried out several other studies have investigated the relationship between biological factors and post-stroke fatigue. Ormstad et al. (2011)

reported that stroke lateralization and infarct volume were not significantly associated with fatigue levels but did report an association between fatigue and patients who had been diagnosed with a stroke of undetermined etiology. This study also found a significant association between fatigue and high cytokine levels and glucose levels. Tang et al. (2013) reported that they found no significant association between fatigue and the number and volume of acute infarcts or the presence of acute infarcts in the frontal lobe, parietal lobe, temporal lobe, occipital lobe, subcortical white matter, globus pallidus, thalamus, mid brain, medulla or cerebellum. This study also found no association between fatigue and the number of old infarcts, white matter hyperintensities, periventricular and deep white matter hyperintensities but did find a significant association between fatigue and the presence of acute infarcts in caudate, putamen and pons. Tang et al. (2014) also found no association between fatigue and the number of acute infarcts or white matter hyperintensities but did find a significant association between higher levels of fatigue and deep cerebral microbleeds. Radman et al. (2012) found no relationship between the location of the lesion and fatigue severity scores. Hubacher et al. (2012) found that patients with subcortical lesions had higher scores on the motor fatigue subscale of the FSMC than patients with cortical lesions and patients with cortical lesions had higher scores on the cognitive fatigue subscale. Finally Huijts et al. (2012) reported that vitamin B12 deficiency was significantly associated with higher levels of fatigue.

Diabetes Mellitus

Two studies reported a significant association between fatigue and diabetes mellitus (Naess et al. 2012; Naess et al. 2005) however another two studies reported no significant association (Tang et al. 2013; Crosby et al. 2012).

Hypertension

One study reported a significant association between fatigue and hypertension or taking anti-hypertensive medication (Harbison, Walsh and Kenny 2009). However another two studies reported no significant association between fatigue and the presence of hypertension (Tang et al. 2014; Tang et al. 2013).

Other factors associated with fatigue after stroke

Studies have investigated associations between fatigue after stroke and a number of other factors. For instance higher levels of fatigue have been found to be associated with migraine (Naess et al. 2005), decreased sexual activity, giving up smoking (Choi-Kwon et al. 2005), being a smoker before stroke (Choi-Kwon et al. 2005), myocardial infarction prior to stroke (Naess et al. 2012), use of anti-depressants, urinary incontinence before stroke (Feigin et al. 2012), life satisfaction (Passier et al. 2011b) and use of sleep medication (Naess et al. 2012; Lerdal et al. 2011).

Multi-variate Analyses

Many of these research studies also performed multi-variate analyses to investigate further which patient characteristics are independently associated with fatigue after stroke and/or how much variance in fatigue scores can be explained by these characteristics (Tang et al. 2014; Lerdal and Gay 2013; Tang et al. 2013; Huijts et al. 2012; Feigin et al. 2012; Eijsden et al. 2012; Parks et al. 2012; Radman et al. 2012; Lerdal et al. 2011; Chestnut 2011; Lewis et al. 2011; Robinson et al. 2011; Zedlitz et al. 2011; Vuletic, Lezaic and Morovic 2011; Mead et al. 2011; Tang et al. 2011; Tang et al. 2010b; Visser-Meily et al. 2008; Jaracz, Mielcarek and Kozubski 2007; van de Port, Kwakkel and Lindeman 2007b; Michael, Allen and Macko 2006; Appelros 2006; Naess et al. 2006; van de Port et al. 2006; Choi-Kwon et al. 2005; Naess et al. 2005; van der Werf et al. 2001; Ingles, Eskes and Phillips 1999).

Unfortunately there was much heterogeneity between these multi-variate models regarding which variables were selected for analysis, the number of variables or whether fatigue score was entered into these models as an independent or dependent variable. Therefore it is difficult to compare or collate the findings from these multi-variate analyses in a meaningful way.

Interventions for Fatigue after Stroke

Currently there is no known treatment for fatigue after stroke. A recent Cochrane review (McGeough et al. 2009) identified three RCTs which investigated potential interventions for fatigue after stroke. One of these RCTs (n = 83) examined whether fluoxetine may improve fatigue after stroke but found it to have no effect. The second RCT investigated whether a neuroprotective agent called tirilazad mesylate would have an effect on the fatigue of female SAH patients. They reported that those in the placebo group were significantly more likely to complain of debilitating fatigue than those in the treatment group. However this was a small study and there were only 9 participants in each group. The third RCT assessed a chronic disease management programme which aimed to teach participants about how to better manage their health, cognitions and emotions. At a six month follow-up assessment they found no significant differences between the fatigue scores of the 67 stroke patients on the programme and the 58 controls.

This Cochrane review also identified two ongoing studies. One of these studies only included patients who complained of sleep disordered breathing and compared fatigue severity scores in those receiving continuous positive airways pressure (n = 15) with those receiving sham continuous positive airways pressure (n = 17). (This study has since been published). The researchers reported that no significant differences in the FSS scores for each of the two groups (Brown et al. 2013).

The other ongoing study mentioned in the Cochrane Review is the Cognitive and Graded Activity Training trial (COGRAT). This study has also now been completed and published (Zedlitz et al. 2012). In this study two interventions were compared to each other. Stroke survivors were randomly allocated to a group which received 12 weeks of cognitive therapy (n = 35) or a group which received 12 weeks of a combination of cognitive therapy and a graded activity programme of treadmill walking and strength training (n = 33). This study reported fatigue scores significantly reduced in both groups and that the group that received the combination of cognitive therapy and graded exercise experienced a greater reduction in fatigue. However a control group was not used so it is not possible to tell whether these interventions were responsible for these reductions in fatigue or whether fatigue levels would have reduced over time without an intervention. An additional problem of this study is that the results could have been confounded by the amount of intervention exposure that participants in each group had. In other words those participants who received GET and CBT may have showed more improvement simply because they were exposed a double intervention rather than because of the content of the interventions

Since this Cochrane review was published a handful more intervention studies have been done. Brioschi et al. (2009) examined the effect of modafinil on subjective fatigue. They reported the severity of fatigue was improved in the patients who had suffered a brainstem or diencephalic stroke (n=10) at 3 months after stroke onset but modafinil had no effect on those who were diagnosed with a control stroke (n=9).

Clarke, Barker-Collo and Feigin (2012) compared the effect of two psycho-education programmes on fatigue. Each programme lasted for six sessions and one was specifically aimed at reducing fatigue. The participants in the fatigue management group were required to keep and review fatigue diaries, undertake educational sessions on fatigue, discuss sleep patterns and fatigue management strategies, consider how exercise affects their fatigue and learn about cognitive behavioural models of fatigue whereas the control group were required to discuss stroke experiences, stroke risk factors, common effects of stroke, how to exercise more poststroke and learn about how to reduce stress and improve nutrition. They reported that participants who were in the fatigue reduction programme (n=9) experienced a greater improvement in fatigue scores than the control group (n=7), however the difference between the groups was not statistically significant.

A recent pilot study tested the effectiveness of a new intervention for the treatment of post-stroke mental fatigue (Hofer et al. 2014). This intervention programme consisted of the participants undertaking a mixture of neuropsychological, psycho-education, cognitive behavioural and mindfulness based therapy sessions. The aims of these therapy sessions were to help participants become more aware of their fatigue, to help them identify factors which lead to their fatigue and to teach the participants ways to manage and cope with their fatigue. This study reported that participants' (n=8) mental fatigue significantly improved after completing the intervention programme. However this study had no control group so it is not possible to determine whether this improvement in mental fatigue was due to intervention.

After reviewing the literature, it is clear that many aspects of post-stroke fatigue have been researched and our knowledge of this topic is growing. However it is also clear that there are still many gaps in this knowledge that need to be filled by further research. It will be discussed in the next section which particular aspects of fatigue after stroke will be investigated further in this thesis.

Review of Fatigue After Stroke Literature Summary

- There is currently no universally accepted definition of fatigue in the stroke literature.
- Fatigue has a detrimental impact on many aspects of a stroke survivor's work, family and social life. Fatigue interferes with rehabilitation and patients report it as being their worst or one of their worst symptoms and that they are not receiving enough help for it.
- There is little consensus in the literature regarding how common fatigue after stroke is. Estimates regarding the prevalence of fatigue range from 23% to 85%.
- The prevalence of fatigue in stroke survivors is consistently reported to be higher than the prevalence of fatigue in healthy age-matched controls.
- Fatigue after stroke is assessed by a variety of multi-item scales, single questions, single items on a large scale, semi-structured interviews and a case definition with associated structured interview.
- Many research studies have investigated which patient characteristics may be associated with fatigue after stroke. The characteristics which have been studied include gender, age, marital status, sleep disorders, disability, stroke severity, pre-stroke fatigue, pain, psychosocial and biological factors. However the only characteristic which has been consistently found to be associated with fatigue after stroke is depression.
- There is currently no effective intervention or treatment for fatigue after stroke.

Section 3 - Post-stroke Fatigue Knowledge Gaps

Identifying which specific aspects of fatigue after stroke should be researched next or exactly how this research should be undertaken can be difficult. In order to aid this decision making process it can be helpful to consult the research regarding fatigue in other conditions as this can provide insight into how the fatigue after stroke research should be taken forward.

Fatigue in conditions other than stroke

Problematic fatigue is common in conditions other than stroke such as multiple sclerosis (MS) (Braley and Chervin 2010; Bol et al. 2009) and cancer (Campos et al. 2011; Hofman et al. 2007). Problematic fatigue has also been reported where a diagnosable medical condition cannot be found. This fatigue is often referred to as chronic fatigue syndrome (CFS) (Brurberg et al. 2014; Christley, Duffy and Martin 2012; Dinos et al. 2009; Fernandez et al. 2009).

There are many similarities between the characteristics of fatigue after stroke and the characteristics of fatigue in MS, cancer and CFS. For instance, the fatigue in these conditions is considered to be a subjective experience (Christley, Duffy and Martin 2012; Campos et al. 2011; Bruera and Yennurajalingam 2010; Mollaoglu and Ustun 2009; Griffith and Zarrouf 2008), is often out of proportion to the amount of previous activity and is not resolved by sleep or rest (Bruera and Yennurajalingam 2010; Ryan et al. 2007; Hofman et al. 2007; Wyller 2007), often exists in the absence of depression (Bol et al. 2009; Stone and Minton 2008; Griffith and Zarrouf 2008) and is considered by sufferers of these conditions as being one of their worst or most distressing symptoms (Berger, Gerber and Mayer 2012; Bol et al. 2009; Mollaoglu and Ustun 2009), which has a very negative impact on their ability to carry out daily activities and their overall quality of life (Fernandez et al. 2009; Bol et al. 2009; Griffith and Zarrouf 2008; Ryan et al. 2007).

Despite these similarities it should not be assumed that fatigue which is reported by MS, cancer or CFS patients is the same as fatigue which is reported by stroke survivors. These conditions each have different aetiologies and patterns of progression therefore fatigue in these conditions may have different aetiologies, treatments, severity levels and may feel qualitatively different from each other to the patient. However examining the research which has been carried out in MS, cancer and CFS may still help to inform the research into post-stroke fatigue. This literature may help fatigue after stroke researchers to better understand how to approach their research. It could provide fatigue after stroke researchers with a starting point from which to decide which aspect of fatigue to research next and may even help with the interpretation of the results of fatigue after stroke studies.

Stroke survivors often have more than one co-morbid condition. Some of these stroke survivors may have MS, CFS, cancer, have recovered from cancer or have another condition which could potentially be causing fatigue. Therefore it is possible that their post-stroke fatigue may be contributed to by having one of these other conditions. This is another reason why it is important to not ignore the research on fatigue in other patient populations.

Knowledge gaps regarding the frequency and natural history of fatigue after stroke

Nearly all of the studies mentioned in the literature review (Table 1.6) determined the presence or absence of fatigue by using a cut-off score on a multi-item scale, a single item or a single question. The problem with this approach is that fatigue is a subjective feeling and how much it matters to a patient can depend on each individual's personal circumstances. Two patients may score the same on one of these scales or answer yes to the single question, yet one patient may feel they have a distressing problem with fatigue and the other patient may feel that fatigue does not interfere with their lives at all (Andrykowski et al. 2005).

An alternative approach which has been taken in the cancer and CFS literature is to use a case definition approach to assess whether a patient fulfils a specific diagnostic criteria which determines whether they have a clinically significant fatigue i.e. fatigue which is a problem to them (Brurberg et al. 2014; Christley, Duffy and Martin 2012; Andrykowski et al. 2005; Sadler et al. 2002).

The advantage of assessing the frequency of fatigue after stroke using a case definition would be to enable clinicians to know how many stroke survivors actually perceive their fatigue to be a problem and therefore would be interested in undertaking an intervention for fatigue should one be developed (Lynch et al. 2007).

Another knowledge gap which needs to be filled is regarding the natural history of fatigue after stroke. Fatigue has been identified to be a persistent symptom in many MS and cancer sufferers (Berger, Gerber and Mayer 2012; Oh and Seo 2011; Campos et al. 2011; Bol et al. 2009; Hofman et al. 2007; Ryan et al. 2007) and CFS can persist for years (Reid et al. 2000) and although MS is a progressive condition and cancer can be cured meaning that direct comparisons between the natural history of fatigue in these conditions and fatigue after stroke should not be made, it still remains plausible that fatigue after stroke may also persist in the long term.   It is important for this knowledge gap to be filled as stroke survivors need to know whether their fatigue is likely to improve over time, stay the same or progressively get worse so they can plan their future e.g. returning to work or resumption of previous leisure activities. Health care professionals need to know how many stroke survivors are likely to be fatigued at different time points so services can be planned accordingly. Researchers need to know whether fatigue starts immediately after stroke and how long it lasts in order to decide how soon after stroke an intervention for fatigue should be delivered (Duncan et al. 2012).

Knowledge gaps regarding the aetiology and potential treatments of fatigue after stroke

The cause of fatigue is a very important gap in the knowledge as understanding the causes might help an effective treatment to be developed. The aetiology of fatigue after stroke is currently unknown and as previously discussed in the literature review, an effective intervention for post-stroke fatigue has still not been found.

Potential causes of fatigue have been researched significantly more in the CFS, MS and cancer literature than in the stroke literature. Even so, the aetiology of fatigue in each of these conditions is still unknown (Induruwa, Constantinescu and Gran 2012; Berger, Gerber and Mayer 2012; Wyller 2007).

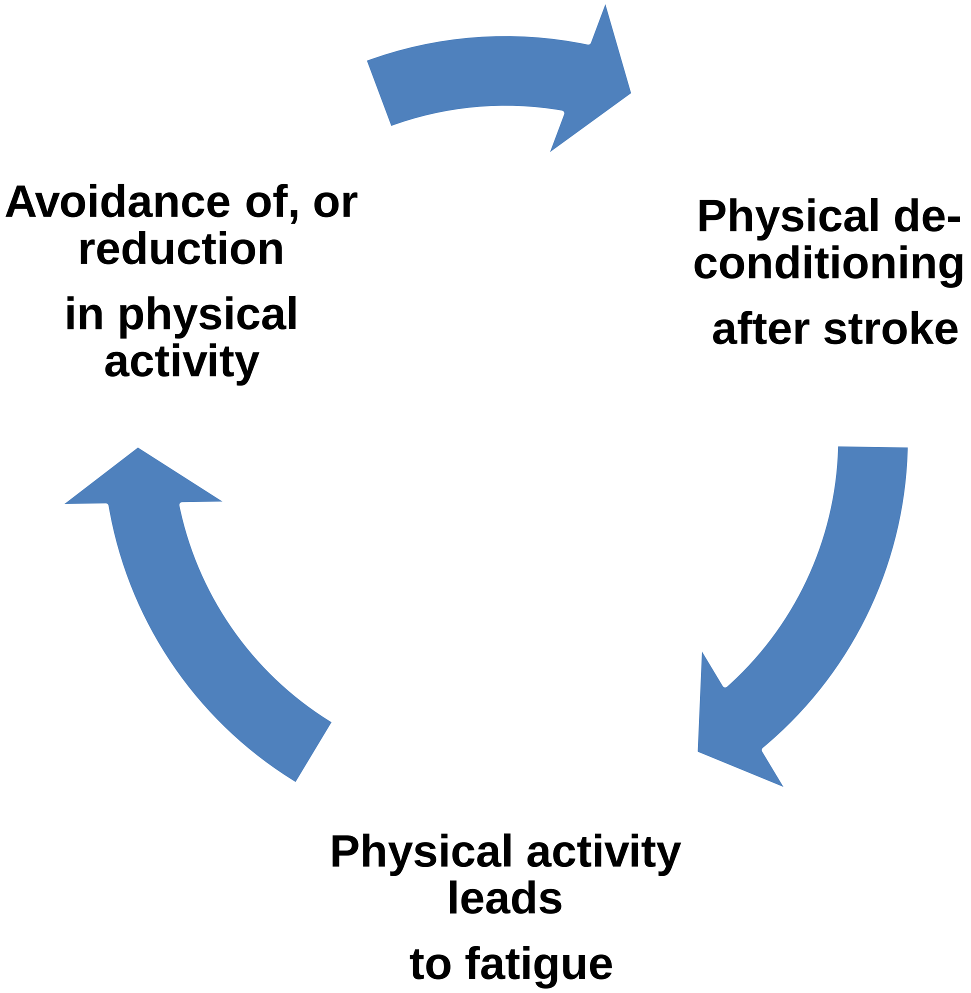
It has been suggested in the CFS, MS and cancer literature that mood disorders such as depression or anxiety may cause, contribute to or perpetuate fatigue and therefore treating depression or anxiety would improve fatigue levels (Bower 2014; Induruwa, Constantinescu and Gran 2012; Wyller 2007). However it is not known whether depression or anxiety may contribute to fatigue in some stroke patients. Several cross-sectional papers have demonstrated an association between fatigue and depression after stroke (Park et al. 2009; Jaracz, Mielcarek and Kozubski 2007; Naess et al. 2005; Choi-Kwon et al. 2005) leading to the suggestion that fatigue is a symptom of post-stroke depression (Stokes, O'Connell and Murphy 2011; Carlsson, Moller and Blomstrand 2003). However, identifying an association between these two symptoms at a particular time point does not necessarily mean that one symptom causes the other, or vice versa; it is equally plausible that a third factor might cause both symptoms (Aldrich 1995). Understanding the direction of causality is important because if depression precedes fatigue then identifying and treating depression might prevent or reduce the risk of developing post-stroke fatigue.

One explanation for the cause of fatigue which has been researched across the CFS, MS and cancer literature is that fatigue may be caused or perpetuated by physical inactivity which is common in people with these conditions (Larun et al. 2015; Pilatti et al. 2013; Latimer-Cheung et al. 2013; Krupp, Serafin and Christodoulou 2010; Stone and Minton 2008). This theory has been referred to as the de-conditioning model of fatigue (Browne and Chalder 2009).

The De-conditioning Model of Fatigue

This model postulates that a reduction in physical activity which is common after stroke as a consequence of reduced mobility causes physical de-conditioning. This reduction in fitness may reduce the body's functional capacity and increase the physical effort required and the perception of the physical effort required to carry out daily tasks. This leads to fatigue being more easily induced during these everyday activities. This additional tiredness then leads to stroke survivors avoiding further activity, which then leads to further de-conditioning. Consequently the stroke survivor may find themselves in a vicious, self-perpetuating cycle of fatigue, avoidance of physical activity, further de-conditioning and more fatigue (Browne and Chalder 2009). This cycle is illustrated in Figure 1.1.

Figure 1.1 – Illustration of the cycle of fatigue, avoiding physical activity, further de-conditioning and more fatigue.



Although it should also be taken into consideration that this cycle of fatigue may not begin with lack of physical activity and de-conditioning. It is also plausible that the cycle may start with the patient being fatigued for unknown reasons soon after stroke onset and this fatigue is what leads to lack of physical activity and de-conditioning which leads to even more fatigue. In other words the direction of causality may be that fatigue causes a reduction in physical activity and de-conditioning instead of lack of physical activity and de-conditioning causing fatigue.

Muscle de-conditioning has previously been found to be associated with fatigue in cancer patients (Bower 2014; Cramp and Byron-Daniel 2012; McMillan and Newhouse 2011), MS patients (Krupp, Serafin and Christodoulou 2010; Johnson 2008) and muscle de-conditioning has been reported in CFS patients (Brown 2014; Wyller 2007). Associations between high levels of fatigue and low levels of activity have been reported in research with MS and cancer patients (Kos et al. 2008; Luctkar-Flude et al. 2007). Moreover, activity and exercise based interventions have been found to be an effective treatment for reducing fatigue in CFS, MS and cancer patients (Larun et al. 2015; Oral and Yaliman 2013; Pilutti et al. 2013; Latimer-Cheung et al. 2013; Cramp and Byron-Daniel 2012; Andreasen, Stenager and Dalgas 2011). In relation to stroke patients one study reported that muscle strength of the leg on both sides is significantly lower in stroke survivors compared with control patients (Carin-Levy 2006). (Although it is possible that the reason leg muscle strength on both sides was lower in this study was not due to de-conditioning after stroke onset but due to a condition or conditions which predate the stroke).

Therefore it is plausible that low activity and muscle de-conditioning may be also be associated with fatigue in stroke patients but sufficient research has not yet been done to establish such a relationship. It is important to establish if an association exists between fatigue and physical activity and/or physical fitness in stroke patients as this would provide a rationale for developing a physical activity-based treatment for fatigue after stroke.

In conclusion, this section has introduced relevant literature on fatigue in cancer, MS and CFS patients and has identified some gaps in the knowledge that will be researched further in this thesis. The next section will present the specific research questions for this thesis and the plan for exactly how these questions will be investigated.

Post-stroke fatigue knowledge gaps summary

- There are several gaps in the knowledge of fatigue after stroke that need to be filled by further research.
- Consulting the literature on CFS, cancer-related fatigue and MS patients can be useful to inform the research on fatigue after stroke.
- Case definitions have been used in CFS, MS and cancer literature.
- Fatigue in CFS, MS and cancer patients can persist for years indicating the possibility that fatigue could also be a long term problem in stroke patients.
- The aetiology of CFS, cancer-related fatigue or fatigue in MS patients is not known.
- One theory postulated in the literature of these conditions is that muscle de-conditioning causes fatigue. This theory is known as the de-conditioning model of fatigue.
- Activity based and exercise treatments have been reported to be effective in CFS, MS and cancer patients for reducing fatigue.
- It is plausible that activity and exercise may help reduce fatigue in stroke patients as well.
- However before exercise trials with stroke patients can be developed, it is important to establish an association between activity and/or fitness and fatigue.

Section 4 – PhD Research Questions and Research Plan

This PhD thesis aims to address these knowledge gaps by asking the following questions:

- What is the frequency and natural history of fatigue, especially *clinicially significant* fatigue, after stroke?
- Is there a temporal relationship between fatigue and mood?
- Is fatigue after stroke associated with lower levels of physical activity?
- Is fatigue after stroke associated with lower levels of physical fitness?

This PhD will attempt to answer these questions by carrying out the following:

- A systematic review of longitudinal studies to evaluate the existing evidence regarding the frequency and natural history of fatigue after stroke and any temporal relationship between fatigue and mood.

  This systematic review is novel as it will focus entirely on longitudinal studies. There are numerous cross-sectional studies in the fatigue after stroke literature, as mentioned previously in the literature review of this thesis, but these studies do not tell us how the frequency of fatigue changes over time or whether anxiety or depression precedes fatigue or vice versa. No systematic review of longitudinal studies of fatigue after stroke has previously been carried out.

- A systematic review to evaluate the existing evidence regarding associations between fatigue after stroke and physical fitness and/or physical activity.

  No such systematic review has been carried out before in stroke patients. This review is an important first stage of investigating the theory that fatigue after stroke may be caused by physical de-conditioning.

- A longitudinal cohort study which will assess:

  -the frequency of clinically significant fatigue at three time points over the first year.

  -the natural history of clinically significant fatigue over the first year including any temporal relationship between mood and fatigue.

  -the physical activity levels of stroke patients at three points over the first year and determine whether they are associated with fatigue.

-physical fitness (leg strength, leg power, hand grip strength, aerobic fitness) levels of stroke patients at three time points over the first year and determine whether they are associated with fatigue.

This longitudinal study will have several novel aspects. It will use a case definition approach to assess the frequency and natural history of fatigue after stroke. This approach to assessing fatigue has not previously been used in the stroke literature. It will be the first longitudinal study in the stroke literature to investigate associations between fatigue and activity and/or fitness and it will include a wider range of activity and fitness measures than has been previously used in a single study. It will also be the first longitudinal study in stroke patients to examine the relationships between mood, fatigue, activity and fitness over different time points.

Chapter 2 – Frequency and Natural History of Fatigue After Stroke: A Systematic Review of Longitudinal Studies

The searches for the systematic review in this chapter were originally done on 7th April 2011 and data resulting from this search have been published in the Journal of Psychosomatic Research (Duncan, Wu & Mead 2012). The full paper has been included as an appendix (Appendix 1). The searches were subsequently updated on 9th January 2015. The results of this updated review are now presented in this chapter.

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Abstract

Background: Fatigue is a common and distressing symptom after stroke. Stroke survivors and health professionals need to know whether fatigue is likely to improve, or get worse over time; and whether there is a temporal association with depression or anxiety, which might provide a target for treatment,

Aims and objectives: to systematically review all longitudinal observational studies which have assessed fatigue on at least two separate time points after stroke onset to determine its frequency, natural history and temporal relationship with anxiety and/or depression.

Method: MEDLINE, EMBASE, CINAHL and PsycInfo were systematically searched using the keywords “fatigue” and “stroke” and their associated terms or synonyms. Data were extracted regarding time points after stroke where fatigue was assessed, frequency of fatigue at each time point and any reported associations with anxiety and/or depression.

Results: Ten studies fulfilled the inclusion criteria. Fatigue was assessed at a variety of time points after stroke (from admission – to 36 months). The frequency of fatigue ranged from 30%-92% at the first time point. Frequency of fatigue declined across time points in seven of the studies (n = 764) and increased in three studies (n = 304). Three papers found significant associations between fatigue and mood at the same time point. The single study investigating temporal associations between fatigue and mood disorders reported that depression predicted subsequent fatigue.

Conclusions: Fatigue is present soon after stroke onset and remains common in the longer term. There is little evidence regarding the temporal relationship between fatigue and mood: this is an area where further research is needed.

Rationale

It was stated in Chapter 1 that this thesis intends to investigate the frequency, natural history of fatigue after stroke and whether fatigue has a temporal relationship with mood. Therefore the purpose of this chapter is to attempt to answer these research questions by evaluating the existing evidence regarding these aspects of fatigue after stroke.

In Chapter 1 (Table 1.6), numerous cross sectional studies of the frequency of fatigue after stroke were presented. Longitudinal studies have major advantages over cross sectional studies when studying the natural history of a condition or symptom because they report changes within individuals as well as the proportion of patients at a particular time point who have a symptom. Therefore longitudinal studies of post-stroke fatigue could reveal if fatigue is a stable symptom or whether it fluctuates over time. Longitudinal studies can also provide information about whether fatigue affects all patients for a short period of time or a small number of patients over an extended period; cross-sectional studies are unable to provide this information (Yee and Niemeier 1996). In addition, longitudinal studies can *potentially* provide evidence regarding the direction of any observed association between fatigue and mood disorders i.e. whether depression precedes fatigue or vice versa (Chaiton et al. 2009).

Several non systematic reviews of fatigue after stroke have been published (Choi-Kwon and Kim 2011; Annoni et al. 2008; Barker-Collo, Feigin and Dudley 2007; Colle et al. 2006; de Groot, Phillips and Eskes 2003; Staub and Bogousslavsky 2001). Systematic reviews are scientifically more robust and are consequently considered to be more objective sources of information and less prone to bias and error than traditional narrative reviews (Egger, Davey Smith and Altman 2001). The single previous systematic review used narrow search terms and so may have missed studies. Furthermore that search was performed in 2009 and other studies on post-stroke fatigue may have been published since then and this review being undertaken (Lerdal et al. 2009).

The aim of this systematic review was to identify all *longitudinal* observational studies of fatigue after stroke to determine the frequency of fatigue, its natural history and the temporal relationship between fatigue and mood disorders.

Method

A detailed protocol specifying the aims and objectives for the review and precisely which studies will be included or excluded was written prior to any searches being carried out (Appendix 2).

Searches

Searches were conducted in MEDLINE (from 1966), EMBASE (from 1980), CINAHL (from 1937) and PsycInfo (from 1806) initially on 7th April 2011 and subsequently updated in MEDLINE, EMBASE and PsycInfo on 9th January 2015 using keywords "fatigue" and "stroke" and their associated terms or synonyms. The same search terms were used in this review as in the published Cochrane systematic review (McGeough et al. 2009) of interventions for post-stroke fatigue (Appendix 3).

Study selection

One reviewer (FD) removed all duplicates using Endnote, and then scrutinised unique titles and their abstracts. Those abstracts that were potentially relevant were obtained as full texts. Reference lists of the retrieved articles where fatigue after stroke was the dominant topic (including reviews, qualitative, cross sectional and longitudinal studies) were scrutinised for further potentially relevant studies. One reviewer (FD) applied the following inclusion criteria to all articles that had been retrieved as full texts; any uncertainties were resolved by discussion with a second reviewer (GM).

The inclusion criteria were:

1) written in English

2) published as a full text article in a peer review journal

3) recruited people with stroke (first or recurrent, ischaemic or haemorrhagic) > 18 years old

4) retained 10 or more participants for the duration of the study

5) specifically assessed and separately reported the presence or absence or fatigue using a single question, a case definition or a specified cut-off on a fatigue scale.

6) assessed fatigue on at least two separate occasions at least one month apart

7) recruited participants prospectively

8) the first measurement of fatigue was not more than 6 months after stroke onset.

Publications were excluded if:

1) they were only published in abstract form

2) they contained no primary data (e.g. reviews, editorials)

3) it was not possible to separately extract data for stroke patients from other types of patient

4) they recruited participants retrospectively

5) they used only an unstructured assessment of fatigue (e.g. qualitative assessments of fatigue where the specific questions asked may have varied from patient to patient)

6) assessed fatigue of patient only by asking carers or relatives.

Data extraction

Two reviewers (FD and SW) independently extracted data onto paper data collection forms for the initial search (Appendix 4) describing a) age, gender, sample size, time since stroke for each follow up, type of stroke b) methods of measuring fatigue and/or mood, total number of participants who completed fatigue assessment at each time point c) number of times fatigue was separately assessed and time between each assessment d) any reported frequencies of fatigue, depression and/or anxiety e) any reported associations between fatigue and anxiety or depression. For the updated search only one reviewer (FD) extracted data.

Data Synthesis

The intention was to perform a meta-analysis in order to ascertain an estimate of the frequency of fatigue at different time points after stroke. However this could not be done due to the heterogeneity between the included studies regarding the time points that fatigue was assessed at, methods of assessing fatigue and populations from which participants were recruited. Instead, details of included studies were tabulated and a narrative data synthesis approach was undertaken.

Methodological Quality assessment

There is no clear consensus amongst researchers regarding which tool to use when assessing the quality of observational studies included in systematic reviews (Mallen, Peat and Croft 2006). The Downs and Black checklist was chosen as the tool for assessing the quality of the studies included in this review as it was developed for use in observational studies as well as randomised trials (Downs and Black 1998). It provides an overall score for study quality and a profile of scores for quality on four separate subscales; quality of reporting, internal validity, power and external validity. Fourteen of the 27 items are applicable to observational studies which do not provide an intervention. All 14 items were applied by one reviewer (FD) and a score of 0 or 1 given for each item.

Results

The original electronic search identified 7046 citations before duplicates were removed. The full texts of 101 potentially relevant papers were retrieved. A further seven papers were retrieved following scrutiny of the reference lists of papers (reviews, qualitative, cross-sectional and longitudinal studies) where the main topic was fatigue after stroke. (Figure 2.1).

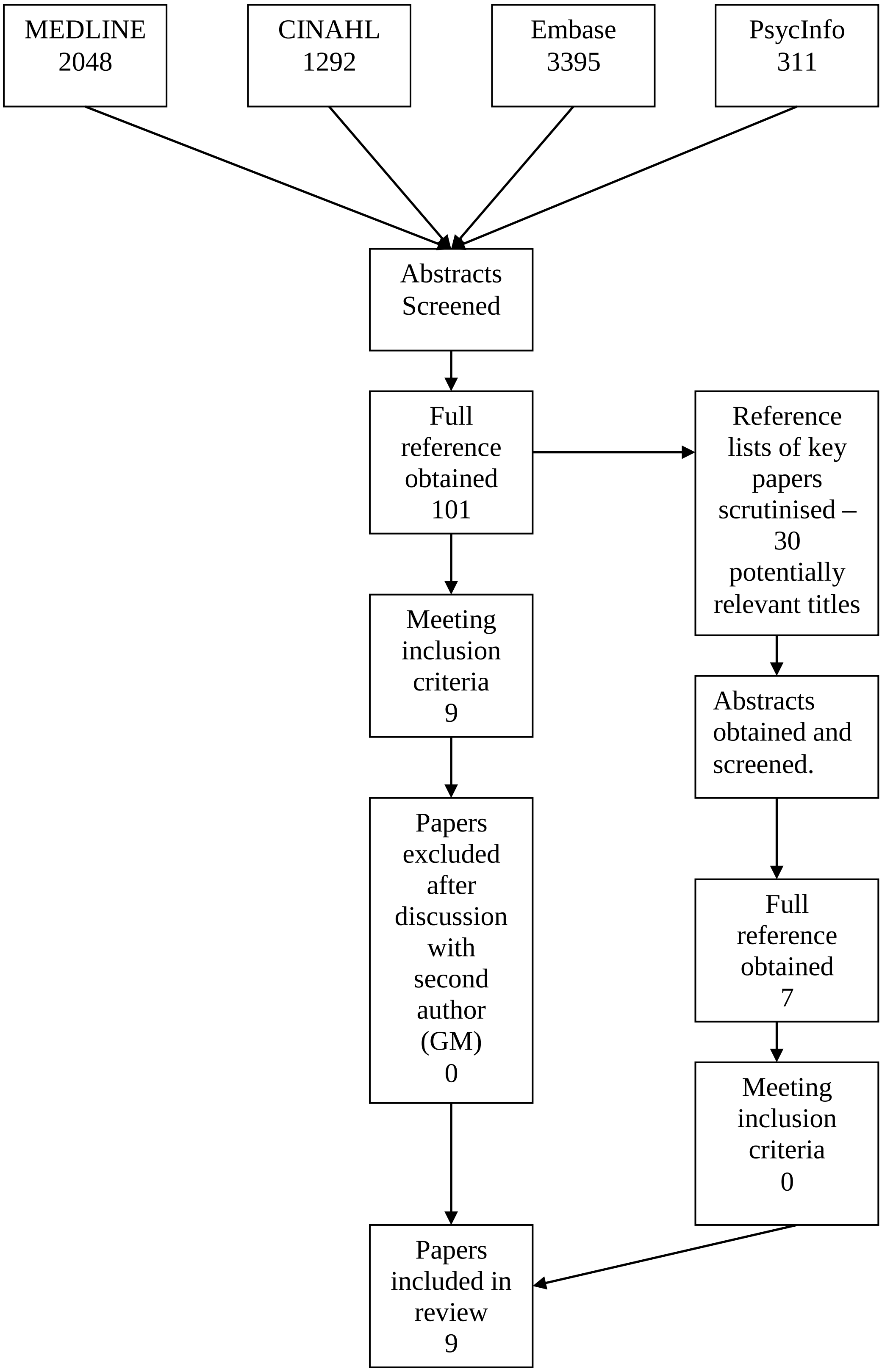


Figure 2.1 – Publication search and selection for original search done on 7th April 2011

Of these 108 papers identified in the original search, 99 were excluded. The main reasons for excluding a study were a) it was a review and contained no original research b) it was cross sectional and fatigue was only assessed at one time point c) it recruited fatigued patients retrospectively d) it mentioned post-stroke fatigue but did not specifically report fatigue data for participants.

The searches identified four studies that nearly met the inclusion criteria. One study (Astrom, Asplund and Astrom 1992) had to be excluded as 12% of the participants had had transient ischaemic attack, rather than stroke and the study did not separately report the data for the stroke patients. Another study was excluded as it reported energy subscale mean scores instead of frequency of fatigue at each time point (Franzen-Dahlin et al. 2010). A third study performed a number of psychosocial measurements on subarachnoid haemorrhage survivors at 3, 9 and 18 months after stroke onset but reported the frequency of fatigue only at the 9 and 18 month time points (Powell et al. 2002, Powell et al. 2004). A study, which was identified in the updated search, was excluded as it assessed fatigue in participants at the time they were being discharged from rehabilitation and 24 weeks later instead of at specified time points (van Eijsden et al. 2012).

Thus, nine studies, recruiting a total of 959 participants fulfilled the inclusion criteria in the original search and the updated search retrieved one further paper (n=99) which fulfilled the inclusion criteria (Table 2.1).

Table 2.1 – Studies assessing fatigue at two or more time points after stroke

	Source of sample	**Pathological Type of Stroke**	**First or recurrent stroke**	**Age (years) Mean (SD), Range or median**	**Gender, number (N) and %.**	**Method of assessing fatigue**	**Time of assessment post stroke and number (N) that completed fatigue measure at each time point.**	**Frequency of fatigue at each time point (95% CI)***	**Differences in fatigue scores across time points (if reported)**
Schepers 2006	Rehabili-tation Centre	Ischaemic 68.9% Haemorrhagic 31.1%	First	56.4 (11.4)	N = 98 (58.7%) Male N = 69 (41.3%) Female	Fatigue Severity Scale	Admission, N=167 6 months, N=167 12 months, N=167	51.5 (43.5-59.5) 64.1 (57.1-71.1) 69.5 (62.5-76.5)	Significantly higher fatigue scores at 1 year than at admission (p<0.000)
Van de Port 2007a	Rehabili-tation Centre	Ischaemic 72.2% Haemorrhagic 27.8%	First	57.3 (11.1)	N = 133 (59.6%) Male N = 90 (40.4%) Female	Fatigue Severity Scale	6 months, N=223 12 months, N=223 36 months, N=223	68 (62-74) 74 (68 – 80) 58 (52- 64)	Not reported
Skaner 2007	Various sources	Ischaemic 78% Haemorrhagic 6% Non-specified stroke 16%	First	73.3 (11.8)	N = 69 (48%) Male N = 76 (52%) Female	Single item on Goteborg Quality of Life Instrument	3 months, N=106 12 months, N=97	69 (60 – 78) 58 (48 - 68)	Significantly lower fatigue scores at 1 year than at 3 months. (p=0.044)
Sisson 1995	Three hospitals	All right hemisphere strokes	First	33-77	N = 6 (46%) Male N = 7 (54%) Female	Single question on Neurobehavio ural Rating Scale. Mental fatigue	1 month, N=13 6 months, N=13	92.3 (78.3-100) 84.6 (64.6- 100)	Not reported
Christensen 2008	Three acute	Ischaemic or haemorrhagic	First	Median 64.5	N=77 (56%)	Multidimensio nal Fatigue	10 days, N=138 3 months, N=138	59 (51-67) 44 (36 – 52)	Significantly lower fatigue scores at 3

	stroke units			IQR 55.8-72.5	Male N = 61(44%) Female	Inventory (MFI-20). General fatigue subscale.	12 months, N=138 24 months, N=138	38 (30 – 46) 40 (32- 48)	months than at 10 days (p<0.0001). No further significant changes between 3 months and 2 years
Snaphaan 2011	Hospital Neuro-logy Depart-ment	Ischaemic	First or recurrent	65 (12.9)	N = 69 (64%) Male N = 39 (36%) Female	Checklist Individual Strength Fatigue Subscale	2 months, N=108 18 months, N=108	35 (26-44) 33 (24- 42)	Not reported
Hellawell 1999	Hospital Neuro-surgical Unit	Subarachnoid Haemorrhage	Not specified	49.7 (14.6)	N = 20 (45.5) Male N = 24 (54.5) Female	Single item on Head Injury Symptom Checklist	6 months, N=28 12 months, N=22 24 months, N=19	64.3 (46.3-82.3) 59.1 (38.1-80.1) 68.4 (47.4-89.4)	Not reported
Ogden 1994	Hospital Neuro-surgery Unit	Subarachnoid Haemorrhage	First	44.7(14.2) Men 46.4 (12.7) Women	N = 59 (33.7%) Male N = 30 (66.3%) Female	Single question – were they more frequently fatigued than before their SAH (yes/no)	10 weeks, N=89 12 months, N=66	88.9 (81.9 – 95.9) 86.2 (78.2-94.2)	Not reported
Noble 2008	Two hospitals	Subarachnoid Haemorrhage	First	52.4	N = 45 (62.9%) Male N = 60 (57.1%) Female	Multidimensional Fatigue Symptom Inventory – Short Form	24-251 days (109 average) N= 73 335-672 days (406 average) N = 87	59 (48 – 70) 36 (26 – 46)	No significant differences in fatigue scores between time 1 and time 2 (p>0.05)

Radman 2012	Hosptial Neuro-logy Depart-ment	Ischaemic or haemorrhagic	First	51.1 (13.8)	66% Male 34% Female	Fatigue Assessment Instrument (FAI)	6 months, N = 109 12 months, N = 99	30 (21.4-38.6) 34 (24.7-43.3)	Not reported

Demographic characteristics

Six studies (n = 746) included patients with ischaemic and haemorrhagic strokes (Radman et al. 2012; Christensen et al. 2008; van de Port et al. 2007a; Skaner et al. 2007; Schepers et al. 2006; Sisson 1995), one (n = 108) included patients only with ischemic strokes (Snaphaan, van der Werf and de Leeuw 2011) and three (n = 204) only included patients with subarachnoid haemorrhage (Noble et al. 2008; Hellawell, Taylor and Pentland 1999; Ogden, Mee and Henning 1994). Seven studies (n = 562) recruited participants from hospitals (Radman et al. 2012; Snaphaan, van der Werf and de Leeuw 2011; Christensen et al. 2008; Noble et al. 2008; Hellawell, Taylor and Pentland 1999; Sisson 1998; Ogden, Mee and Henning 1994), two (n = 390) from rehabilitation centres (van de Port et al. 2007a; Schepers et al. 2006), and one (n = 106) recruited from several sources (Skaner et al. 2007). Eight studies (n=922) only included first ever strokes (Radman et al. 2012; Christensen et al. 2008; Noble et al. 2008; van de Port et al. 2007a; Skaner et al. 2007; Schepers et al. 2006; Sisson 1995; Ogden, Mee and Henning 1994), one (n = 108) included first or recurrent strokes (Snaphaan, van der Werf and de Leeuw 2011) and one (n = 28) did not specify which types of stroke were included (Hellawell, Taylor and Pentland 1999). The mean age of the participants ranged from 45.5 years (Ogden, Mee and Henning 1994) to 73.3 years (Skaner et al. 2007). The proportion of males ranged from 33.7% (Ogden, Mee and Henning 1994) to 66% (Radman et al. 2012).

Assessment of fatigue

A variety of instruments were used to assess fatigue: two studies used the Fatigue Severity Scale (FSS) (van de Port et al. 2007a; Schepers et al. 2006), one used the Multidimensional Fatigue Inventory (MFI-20) (Christensen et al. 2008), one used the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) (Noble et al. 2008), one used the Checklist Individual Strength Fatigue Subscale (Snaphaan, van der Werf and de Leeuw 2011), one used the Fatigue Assessment Instrument (FAI) (Radman et al. 2012) and the remaining four studies either used either a single question (Sisson 1995; Ogden, Mee and Henning 1994) or a single item from a longer instrument (Skaner et al. 2007; Hellawell, Taylor and Pentland 1999).

Methods used for assessing fatigue

Multi-item scales

Six papers used multi-item scales for assessing fatigue. There are slight differences regarding exactly what each multi-item scale measures. The FSS concentrates on how fatigue impacts on the daily life of a stroke survivor. The items on the CIS and the general fatigue subscale of the MFI-20 are very similar and assess symptoms that could be categorised as physical fatigue. The FAI aims to determine the severity and consequences of fatigue. The fourth multi-item scale, the MFSI-SF is more diverse. It consists of five subscales; general fatigue, emotional fatigue, mental fatigue, physical fatigue and vigour from which an overall score is calculated.

The two studies that used the FSS used very similar cut-off scores for fatigue. On the FSS, participants respond on a 7 point scale to nine statements and their score is the mean of all nine items. One study had a cut-off score of above 4 (Schepers et al. 2006) and the other used a cut-off score of equal to or more than 4 (van de Port et al. 2007a). The other four scales all use a different scoring system so it is not possible to directly compare the cut-off scores of these multi-item scales to each other. However it is possible to compare the labels that each study attributed to patients who scored above their respective cut-off score and these labels did differ quite significantly. One study labelled those above their specified cut-off as “having a moderate to high impact of fatigue” (Schepers et al. 2006, p185), another labelled patients as “fatigued” (van de Port et al. 2007a, p41), two studies reported that scoring above the cut-off point was indicative of "severe fatigue” (Radman et al. 2012, p 1425; Snaphaan, van der Werf and de Leeuw 2011, p612), another that it was indicative of an "abnormal" or "pathological" fatigue” (Noble et al. 2008, p1098), the final study labelled those scoring above the cut-off score as “suffering from a clinically significant pathological fatigue” (Christensen et al. 2008, p136).

In addition to there being a lack of consensus regarding how to label fatigue scores above a cut-off point, as previously mentioned, it should also be taken into consideration that using cut-off scores to analyse data may have over-simplified the data which may have resulted in losing some information about how the natural history of fatigue changes over time.

In both the studies that used the FSS, the mean score at 12 months was 4.7 indicating that fatigue severity is similar across both these samples (van de Port et al. 2007a; Schepers et al. 2006).

Single question or single item assessments

Four papers used a single item or a single question to assess fatigue (Skaner et al. 2007; Hellawell, Taylor and Pentland 1999; Sisson 1995; Ogden, Mee and Henning 1994). Each question or item in these studies was slightly different. Two of the included studies presented stroke survivors with a list of symptoms which included fatigue. In one study participants were asked to indicate which symptoms they had experienced recently (Hellawell, Taylor and Pentland 1999). In the second study participants were asked to indicate which symptoms they had been troubled by recently (Skaner et al. 2007). In the third study participants were asked if they were frequently more fatigued than before their stroke and they answered either yes or no (Ogden, Mee and Henning 1994). The fourth study used the Neurobehavioural Rating Scale which involves a clinician interviewing each participant for 15-20 minutes. One item on the scale concerns fatiguability. The clinician observes the participant during the interview and makes a judgement regarding the participant's fatiguability during tasks or whether they appeared lethargic (Sisson 1995).

Timing of fatigue assessments

Six studies (n = 502) assessed fatigue at two time points (Radman et al. 2012; Snaphaan, van der Werf and de Leeuw 2011; Noble et al. 2008; Skaner et al. 2007;

Sisson 1995; Ogden, Mee and Henning 1994), three (n = 418) at three time points (van de Port et al. 2007a; Schepers et al. 2006; Hellawell, Taylor and Pentland 1999) and one (n = 138) assessed fatigue at four separate time points (Christensen et al. 2008). A variety of time points were used to assess fatigue. First assessments of fatigue were carried out at admission in one study (n = 167) (Schepers et al. 2006), 10 days (n = 138) (Christensen et al. 2008), one month (n = 13) (Sisson 1995), 10 weeks (n = 89) (Ogden, Mee and Henning 1994), 2 months (n = 108) (Snaphaan, van der Werf and de Leeuw 2011), 3 months (n = 106) (Skaner et al. 2007), 6 months (n = 350) (Radman et al. 2012; van de Port et al. 2007a; Hellawell, Taylor and Pentland 1999) and mean of 109 days (n = 79) after stroke (Noble et al. 2008). Two assessed fatigue at 3 months (n = 244) (Christensen et al. 2008; Skaner et al. 2007), four at six months (n = 431) (van de Port et al. 2007a; Schepers et al. 2006; Hellawell, Taylor and Pentland 1999; Sisson 1995), seven at 12 months (n = 812) (Radman et al. 2012; Christensen et al. 2008; van de Port et al. 2007a; Skaner et al. 2007; Schepers et al. 2006; Ogden, Mee and Henning 1994; Hellawell, Taylor and Pentland 1999), one at 18 months (n = 108) (Snaphaan, van der Werf and de Leeuw 2011) and two at 24 months (n = 157) (Christensen et al. 2008; Hellawell, Taylor and Pentland 1999). No two studies assessed fatigue at the same combination of time points.

Time course of fatigue

Seven of the studies (total n = 764) reported that the proportion of patients with fatigue decreased over time (Snaphaan, van der Werf and de Leeuw 2011; Christensen et al. 2008; Noble et al. 2008; van de Port et al. 2007a; Skaner et al. 2007; Sisson 1995; Ogden, Mee and Henning 1994). Only three studies (n = 294) reported that it increased over time (Radman et al. 2012; Schepers et al. 2006; Hellawell, Taylor and Pentland 1999).

Four studies reported whether there was a statistically significant difference in fatigue scale scores between time points. One study (n= 167) reported that fatigue scores were significantly higher as time went on (Schepers et al. 2006), whereas two studies (n = 244) found fatigue scores to be significantly higher at the first time point (Christensen et al. 2008, Skaner et al. 2007) and the other study (n=87) found no significant differences in fatigue scores across the time points (Noble et al. 2008).

Course of fatigue after stroke for individual patients

Four studies investigated whether it was the same participants who were fatigued or not fatigued across all time points or whether a more complex course of fatigue exists for each individual (Radman 2012; Snaphaan, van der Werf and de Leeuw 2011; Christensen et al. 2008; Schepers et al. 2006). One of these studies (n = 167) reported that fatigue was present at all three time points in 37.7% of participants and was absent at all three time points in 17.4% of participants (Schepers et al. 2006). Another study (n = 108) found that 57% of patients did not have fatigue at any time point and 26% had fatigue at both time points. This study also reported that 9% had recovered from their fatigue between two and 18 months post stroke and 8% had developed fatigue between two and 18 months post stroke (Snaphaan, van der Werf and de Leeuw 2011). The third study (n = 138) reported that fatigue was a stable symptom with 72% of their participants remaining either fatigued or non-fatigued between 10 days and three months and 75% between three months and two years.

This study also reported that only 9% of participants developed fatigue between three months and two years (Christensen et al. 2008). Finally, one study (n = 99) reported that of the patients who reported fatigue at the 6 month time point, 77.3% still reported fatigue at the 12 month time point (Radman et al. 2012).

Relationship between fatigue and mood

The second aim of this systematic review was to explore the temporal relationship between fatigue and mood. Nine of the included studies assessed depression and/or anxiety. Four of these studies (Skaner et al. 2007; Hellawell, Taylor and Pentland 1999; Sisson 1995; Ogden, Mee and Henning 1994) reported the frequency of depression at each time point but did not report any associations between depression and fatigue. One study did not report the associations between fatigue and mood but commented that depression may be a confounder of the relationship between fatigue and health related quality of life (van de Port et al. 2007a). The remaining four studies (n = 99, 167, 138, 87) reported data on the relationship between fatigue and mood (Radman et al. 2012; Snaphaan, van der Werf and de Leeuw 2011; Noble et al. 2008; Schepers et al. 2006) (Table 2.2).

Table 2.2 – Longitudinal cohort studies reporting associations between mood and fatigue after stroke.

Paper	Method of measuring depression and/or anxiety	Method of measuring fatigue	Associations between mood and fatigue after stroke	Additional evidence that depression and/or anxiety precedes fatigue.
Schepers 2006	Center of Epidemiologic studies depression scale (CES-D)	Fatigue Severity Scale	Depression at one year is associated with fatigue at one year ($p<0.001$)	None reported
Snaphaan 2011	Hospital Anxiety and Depression Scale (HADS)	Checklist for Individual Strength Fatigue Subscale	Higher levels of depression and anxiety at baseline were significantly associated with fatigue at baseline ($p<0.01$, adjusted for age and gender)	Patients with fatigue at follow up but not at baseline had higher depression scores at baseline than patients without fatigue at both time points. (OR 1.32; 95% CI 1.04-1.69 per each point increase on the HADS depressive symptoms items). Higher levels of depression ($p<0.01$) and anxiety ($p=0.03$) at baseline were significantly associated with fatigue at follow up (adjusted for age and gender)

Noble 2008	Post-traumatic stress diagnostic scale	Multidimensional Fatigue Symptom Inventory	At the first time point, PTSD symptom severity scale scores were significantly associated with total fatigue scores at time point 1(R squared = 0.49, beta=0.786, p<0.0001). At the second time point, PTSD symptom severity scale scores were significantly associated with total fatigue scores at assessment 2 (R squared = 0.58, beta = 0.796, p<0.0001)	None reported
Radman 2012	Hamilton Depression Rating Scale (HDRS) Hamilton Anxiety Rating Scale (HARS)	Fatigue Assessment Instrument (FAI)	At the six month time point, fatigue severity was significantly independently associated with anxiety scores. (OR 1.331; 95% CI 1.161-1.527; p < 0.0001) This was still the case even when only non-depressed participants (OR 1.562; 95% CI 1.211-2.013; p = 0.001) or only non-retired participants were taken into account (OR 1.329; 95% CI 1.121-1.576; p = 0.001) At the 12 month time point, fatigue severity was significantly independently associated with higher levels of depression (OR 1.332; 95% CI 1.141-1.554; p < 0.0001) This was still the case even when only non-depressed participants (OR 1.561; 95% CI 1.221-1.994; p < 0.0001) or only non-retired participants were taken into account (OR 1.287; 95% CI 1.094-1.514; p = 0.002).	None reported.

PTSD = Post Traumatic Stress Disorder

All four of the studies reported that depression and/ or anxiety were significantly associated with fatigue, when fatigue and mood were assessed at the same time point (Radman et al. 2012; Snaphaan, van der Werf and de Leeuw 2011; Noble et al. 2008; Schepers et al. 2006). Only one study reported the temporal relationship between mood and fatigue (Snaphaan, van der Werf and de Leeuw 2011). This study reported that higher depression and / or anxiety scores at two months after stroke onset predicted higher fatigue scores at 18 months after stroke onset. This study also found that participants who were depressed at two months, but not fatigued, went on to develop fatigue by the 18 month follow up. This suggests that, in this cohort depression preceded fatigue.

Methodological Quality

The total scores on the Downs and Black (1998) quality assessment checklist ranged from 9-13 with a median score of 11.5 out of a maximum score of 14. The checklist identified weaknesses in each of the three subscales of Reporting, External Validity and Internal Validity (Table 2.3). Seven studies (Radman et al. 2012; Snaphaan, van der Werf and de Leeuw 2011; Christensen et al. 2008; van de Port et al. 2007a; Schepers et al. 2006; Hellawell, Taylor and Pentland 1999; Ogden, Mee and Henning 1994) did not describe the characteristics of participants that had been lost to follow up and five of these studies (Radman et al. 2012; Snaphaan, van der Werf and de Leeuw 2011; Christensen et al. 2008; Schepers et al. 2006; Ogden, Mee and Henning 1994) did not take into account these losses when performing their statistical analyses. Six studies (Snaphaan, van der Werf and de Leeuw 2011; Noble et al. 2008; van de Port et al. 2007a; Schepers et al. 2006; Hellawell, Taylor and Pentland 1999; Sisson 1995) did not report the proportion of eligible patients who agreed to take part. This means that it is difficult to determine whether their sample is representative of the entire population from which they were recruited.

Table 2.3 – Relevant items on Downs and Black (1998) quality assessment checklist and which studies included in the review did not fulfil the item.

Items on checklist relevant to included studies (Downs and Black, 1998, p382-384)	**Christensen 2008**	**Hellawell 1999**	**Noble 2008**	**Ogden 1994**	**Schepers 2006**	**Sisson 1995**	**Skaner 2007**	**Snaphaan 2011**	**Van de Port 2007a**	**Radman 2012**
Reporting Subscale										
"Is the hypothesis /aim /objective of the study clearly described?"	√	√	√	√	√	√	√	√	√	√
"Are the main outcomes to be measured clearly described in the Introduction or Methods section?"	√	√	√	√	√	√	√	√	√	√
"Are the characteristics of the patients included in the study clearly described?"	√	√	√	√	√	√	√	√	√	√
"Are the main findings of the study clearly described?"	√	√	√	√	√	**X**	√	√	√	√
"Does the study provide estimates of the random variability in the data for the main outcomes?"	√	**X**	√	**X**	√	**X**	**X**	√	√	√
"Have the characteristics of patients lost to follow-	**X**	**X**	√	**X**	**X**	√	√	**X**	**X**	**X**

up been described?"										
"Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?"	√	√	√	**X**	√	√	√	√	**X**	√
External Validity Subscale										√
"Were the subjects asked to participate in the study representative of the entire population from which they were recruited?"	√	√	√	√	√	**X**	√	√	**X**	√
"Were those subjects who were prepared to participate representative of the entire population from which they were recruited?"	√	**X**	**X**	√	**X**	**X**	√	**X**	**X**	√
Internal Validity subscale - bias										√
"If any of the results of the study were based on "data dredging" was this made clear?"	√	√	√	√	√	√	√	√	√	√
"Were the statistical tests used to assess the main outcomes	√	√	√	√	√	**X**	√	√	√	√

appropriate?"										
"Were the main outcome measures used accurate (valid and reliable)?"	√	√	√	√	√	√	√	√	√	√
Internal Validity subscale – confounding (selection bias)										√
"Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?"	√	√	√	**X**	√	√	√	√	√	√
"Were losses of patients to follow-up taken into account?"	**X**	√	√	**X**	√	√	√	**X**	√	**X**

X = Study which did NOT fulfil quality for this item or it was not possible to determine from paper.
√ = Study did fulfil quality for this item

Discussion

This systematic review of longitudinal studies of post-stroke fatigue has demonstrated that the frequency of fatigue varied substantially between studies, with estimates ranging from 30% - 92% at first time point, probably reflecting the heterogeneity between the studies regarding the methods of recruitment and their methods of assessing fatigue. This wide range of estimates could also have been caused by chance as most of the studies were not very large and therefore had wide 95% confidence intervals.

Fatigue appears to be a persistent symptom after stroke at least for the first 36 months. The proportion of patients with fatigue at the beginning and end of each study was similar and the fatigue levels of individuals mostly remained stable over time.

This study sought evidence of a temporal relationship between mood and fatigue. Only one included study reported this relationship and demonstrated that those who developed fatigue over time were more depressed at baseline than those who did not develop fatigue at long term follow up suggesting that in some individuals depression predicts subsequent fatigue (Snaphaan, van der Werf and de Leeuw 2011). However as this study was a longitudinal design and not a RCT it is not possible to conclude that depression *causes* subsequent fatigue. Temporal associations between fatigue and depression have been reported in several studies on fatigue in MS and cancer (Patrick, Christodoulou and Krupp 2009; Brown and

Kroenke 2009). However this research has not been able to reach a consensus on whether depression causes fatigue, fatigue causes depression, the relationship is bi-directional or whether a third unknown factor is responsible for both.

Two longitudinal studies which did not specifically meet the review's inclusion criteria as they either did not report the frequency of fatigue at any specific time point (Lerdal and Gay 2013) or only reported the frequency of fatigue at one time point (Passier et al. 2011a) did report evidence regarding temporal associations between fatigue and mood. One study (n = 96) reported that fatigue in the acute period was not associated with mental health at 18 months and that mental health in the acute phase was not significantly associated with fatigue at 18 months after stroke onset, implying that mental health problems do not cause fatigue or are caused by fatigue over this time frame (Lerdal and Gay 2013). The other study (n = 108) reported that participants with depressive symptoms and/or anxiety at three months post stroke onset had significantly higher fatigue scores at 12 months post-stroke than those without depressive symptom or anxiety at three months (Passier et al. 2011a) which implies that, in this group of patients, mood problems may precede fatigue. However in this study it cannot be determined whether these patients did not already have fatigue at the three month time point as it was not assessed until one year post-stroke.

The results of this systematic review are similar to previous reviews in that they also reported post-stroke fatigue to be a common complaint and that its frequency varied between studies (Choi-Kwon and Kim 2011; Lerdal et al. 2009; Annoni et al. 2008;

Barker-Collo, Feigin and Dudley 2007; Colle et al. 2006; de Groot; Phillips and Eskes 2003; Staub and Bogousslavsky 2001). These previous reviews also reported that fatigue is associated with mood. In two of the reviews (Annoni et al. 2008; Barker-Collo, Feigin and Dudley 2007), the only longitudinal paper that was discussed was the study that reported fatigue prevalence to increase over time (Schepers et al. 2006), whereas our review showed that fatigue prevalence decreased over time in seven out of the ten included studies. The only other systematic review of post-stroke fatigue (Lerdal et al. 2009) identified just three longitudinal studies (Christensen et al. 2008; van de Port et al. 2007a; Schepers et al. 2006). None of the previous reviews contained a discussion on the potential temporal association between fatigue and mood.

Previous reviews did not specify whether they included or excluded subarachnoid haemorrhage (SAH) patients in their definition of stroke. For this systematic review we chose to include studies that assessed fatigue in SAH patients. It could be argued that these patients should not have been included because they are not directly comparable to intracerebral haemorrhage and ischaemic stroke patients because SAH has a different aetiology, risk factor management and affects a younger age group. However the aetiology and mechanisms of post-stroke fatigue are not yet understood and SAH patients still have many factors in common with other stroke patients such as sudden onset of disease, long term disabilities and the psychological distress of the event. In addition to this, it would not have been possible to exclude fatigue data for all SAH patients included in our review as three studies (Christensen et al. 2008; Schepers et al. 2006; Sisson 1995) did not specify whether SAH was included or excluded from their sample and one study (van de Port et al. 2007a) reported that they did include SAH patients but it was not possible to separate fatigue data for these patients from other stroke patients in their sample.

Strengths of this systematic review

This review focused on three questions that are of critical importance to stroke survivors. It used a rigorously developed protocol with clearly pre-specified inclusion and exclusion criteria which were agreed in advance of performing the searches. Numerous synonyms of the words "fatigue" and "stroke" were used in the search. Furthermore two authors independently extracted data from papers identified during the original search.

Limitations

Study and Outcome Level Limitations

One limitation which affects the outcome of this review is the heterogenity between the included studies regarding the time points that fatigue was assessed at, methods of assessing fatigue and populations from which participants were recruited. This means that the studies are not directly comparable and this increases the risk of bias regarding the study's findings.

The Black and Downs quality assessment tool (Downs and Black 1998) demonstrated limitations of the studies included in the review. Seven studies

(Radman et al. 2012; Snaphaan, van der Werf and de Leeuw 2011; Christensen et al. 2008; van de Port et al. 2007a; Schepers et al. 2006; Hellawell, Taylor and Pentland 1999; Ogden, Mee and Henning 1994) did not describe the characteristics of the participants who were lost to follow up. It is possible that patients with more severe fatigue may have been more likely to have dropped out and this may have led to an underestimation of fatigue frequency at later time points. On the other hand those who were fatigued at the first time point may have been *less* likely to drop out as they may have wished to continue to participate in research and this would have led to the frequency of fatigue being overestimated at later time points. Six studies (Snaphaan, van der Werf and de Leeuw 2011; Noble et al. 2008; van de Port et al. 2007a; Schepers et al. 2006; Hellawell, Taylor and Pentland 1999; Sisson 1995) did not report the proportion of eligible patients agreeing to take part, and so the sample may not be representative of all strokes. Therefore these studies could be considered to have a high risk of bias.

In addition, two of the studies (Hellawell, Taylor and Pentland 1999; Sisson 1995) included small samples sizes (n= 13, 28) which means they provide a lower precision estimate of the frequency of fatigue, four studies (Skaner et al. 2007; Hellawell, Taylor and Pentland 1999; Sisson 1995; Ogden, Mee and Henning 1994) used a single question to assess fatigue which may not be an adequate method of measuring a multidimensional construct, and two studies (van de Port et al. 2007a; Schepers et al. 2006) recruited participants only from rehabilitation centres which means this sample may not be relevant to those with minor strokes.

Review-level limitations

Although a wide range of synonyms for fatigue were used in our search strategy (e.g. asthenia, lethargy, weariness, exhaustion, lassitude, listlessness, malaise), words such as energy or vitality were not included unless they were preceded by the words “low” or “lack of”. Thus studies which assessed fatigue using an energy subscale of a quality of life instrument e.g. the vitality scale of the SF-36 may have been missed. In addition, a limitation of the Embase search strategy was that a "NOT" operator was used in relation to the names of several other conditions e.g. hepatitis, dialysis, cancer, carcinoma, meningitis, heat stroke, cerebral palsy etc. This potentially could have led to relevant papers being excluded as they may have investigated these patient populations as well as stroke patients. However these scenarios are unlikely as reference lists of key papers were carefully scrutinised to help ensure that we did not miss studies that fulfilled our inclusion criteria.

It was pre-specified that only studies published in the English language would be included. In theory relevant studies published in other languages may have been missed. However all foreign language papers identified by the search had English abstracts and based on scrutinisation of the English abstracts, none of them would have fulfilled the inclusion criteria.

Another limitation of this review is that study selection was carried out by the only one person (FD), but a second researcher was available to discuss any uncertainties about whether to include or exclude studies. The assessment of the quality of the studies was also performed by one researcher but it is highly unlikely that the results of the review would have changed substantially should a second researcher have also assessed quality.

Conclusion

Fatigue is a common symptom post-stroke and is likely to persist in the long term for patients who develop it.   This review explored the possibility of depression and/or anxiety being a cause of fatigue but found insufficient evidence in the literature.

The frequency and natural history of fatigue after stroke will be explored further in Chapter 4 of this thesis and any associations between mood and fatigue will be explored further in Chapter 5.

Summary of Chapter 2

Background and aims

- Stroke survivors and health professionals need to know whether fatigue is likely to improve, or get worse over time; and whether there is a temporal association with depression or anxiety, which might provide a target for treatment.

- This chapter aimed to systematically review all longitudinal observational studies which have assessed fatigue on at least two separate time points after stroke onset to determine its frequency, natural history and temporal relationship with anxiety and/or depression.

Method

- The databases MEDLINE, EMBASE, CINAHL and PsycInfo were systematically searched using the keywords “fatigue” and “stroke” and their associated terms or synonyms.

- Data were extracted regarding time points after stroke where fatigue was assessed, frequency of fatigue at each time point and any reported associations with anxiety and/or depression.

Results

- Ten studies fulfilled our inclusion criteria.
- Fatigue was assessed at a variety of time points after stroke (from admission

– to 36 months).

- The frequency of fatigue ranged from 30%-92% at the first time point. Frequency of fatigue declined across time points in seven of the studies (n = 764) and increased in three studies (n = 294).
- Four papers found significant associations between fatigue and mood at the same time point.
- The single study investigating temporal associations between fatigue and mood disorders reported that depression predicted subsequent fatigue.

Conclusions

- Fatigue is present soon after stroke onset and remains common in the longer term. There is little evidence regarding the temporal relationship between fatigue and mood.

Chapter 3 – Fatigue after stroke: a systematic review of associations with impaired physical fitness.

The searches for the systematic review in this chapter were originally done on 4th November 2010 and data resulting from this search have been published in the International Journal of Stroke (Duncan et al. 2012). The full paper has been included as an appendix (Appendix 5). The searches were subsequently updated on 9th January 2015. The results of this updated review are now presented in this chapter.

This work was supported by the Chief Scientist Office of the Scottish Government.

Abstract

Background: Fatigue is a common and distressing symptom after stroke. Fatigue after stroke might be triggered by physical de-conditioning which sets up a vicious, self-perpetuating cycle of fatigue, avoidance of physical activity, further de-conditioning and more fatigue. If an association between physical activity and fatigue after stroke could be established this would provide a rationale for developing a physical activity based treatment.

Aims: to systematically review all observational studies which have measured both fatigue post stroke *and* one or more measures of physical fitness and/or physical activity at the same time point and reported the association between fatigue and fitness variables.

Method: Publications were identified by systematically searching databases MEDLINE, EMBASE, CINAHL, PsycInfo and Sportdiscus using keywords "fatigue", "stroke", "fitness" or "activity" and their associated terms or synonyms. Publications that provided data on associations between fatigue in stroke patients and levels of physical activity, cardio-respiratory fitness and/or muscle strength and mass were included.

Results: Eight studies fulfilled the inclusion criteria. Only two of these studies found a statistically significant relationship between post-stroke fatigue and either physical activity and/or physical fitness. One study did find, through structural equation modelling techniques that fatigue indirectly influences exercise through self efficacy expectations.

Conclusions: there is very limited evidence regarding associations between exercise, fitness and fatigue after stroke. It still remains highly plausible that exercise can have a positive influence on fatigue.

Rationale

It was stated in Chapter 1 that this thesis also intends to investigate whether fatigue after stroke is associated with lower levels of physical activity and/or physical fitness. Therefore the purpose of this chapter is to identify and evaluate any existing evidence of a relationship between fatigue after stroke and physical activity and/or physical fitness by carrying out a systematic review in order to attempt to answer these research questions.

The aim of this systematic review was to identify all cross sectional and longitudinal observational studies which measured both fatigue post stroke *and* one or more measures of physical activity and/or physical fitness at the same time point and reported the association between fatigue and activity and/or fitness variables.

Method

A detailed review protocol specifying the aims and objectives for the review and precisely which studies would be included or excluded was written prior to any searches being carried out (Appendix 6).

Procedure

Searches were conducted in MEDLINE (from 1966), EMBASE (from 1980), CINAHL (from 1937), PsycInfo (from 1806) and Sportdiscus (from 1800) initially on 4th November 2010 but subsequently updated on 9th January 2015 in MEDLINE, EMBASE and PsycInfo using the keywords “fatigue”, “stroke”, “fitness” or “activity” and their associated terms or synonyms. (Appendix 7).

Potentially relevant papers were identified from their title and abstract and exported to Endnote. After duplicates were removed, every abstract was read and the full text of papers that potentially met the inclusion criteria were obtained. Reference lists of the retrieved articles were scrutinised for further potentially relevant studies. The following inclusion criteria were applied to the retrieved articles: 1) written in English 2) published in a peer reviewed journal 3) recruited people with stroke (first or recurrent, ischaemic or hemorrhagic) > 18 years 4) retained 10 or more participants 5) specifically assessed the presence or absence of fatigue using a single question, a case definition or a specified cut-off on a fatigue scale; or reported fatigue scores as a continuous variable and 6) provided data on associations between fatigue in stroke patients and levels of physical activity, cardio-respiratory fitness and/or muscle strength and mass. Any disagreement about inclusion was discussed with both second reviewers (Professor Gillian Mead and Dr Mansur Kutlubaev) for the initial search and then with Professor Gillian Mead for the updated search.

Papers were excluded if: 1) they were only published in abstract form 2) they contained no primary data (e.g. reviews, editorials etc) 3) it was not possible to separately extract data for stroke patients from other types of patient.

Data extraction – Two reviewers (FD and MK) independently extracted data onto paper data collection forms (Appendix 8) describing a) age, gender, sample size, time since stroke, type of stroke. b) method(s) of measuring fatigue c) method(s) of measuring physical activity and/ or fitness d) results of fatigue and physical fitness and physical activity measures and e) any association reported between fatigue and either physical activity or physical fitness. For the updated search only one reviewer (FD) extracted data.

Data synthesis – the original intention was to perform a meta-analysis to synthesise the relative risks but the data were too diverse to allow for this. Instead a narrative data synthesis approach was chosen.

Definitions

For this review associations between amount of physical activity performed by a stroke survivor and not papers that reported activity limitations were being sought. Physical activity was defined as "all bodily movement that is produced by the contraction of skeletal muscle and that substantially increases energy expenditure". (US Department of Health and Human Services 1996, p21). For instance, studies were included that reported stroke survivors' walking, running, cycling, swimming, playing sports, housework or gardening but studies were excluded that used gait or changes in gait patterns, single limb activity, sitting to standing, toileting or bathing or weight bearing therapy as measures of physical activity. Studies were also excluded if activity was measured by an activities of daily living scale such as the Nottingham Activities of Daily Living scale (Nouri and Lincoln 1987) or the Frenchay Activities Index (Schuling et al. 1993) as several items on these scales refer to activities which do not meet this study's definition of physical activity such as reading books, writing letters, driving a car, taking a car ride or participating in gainful work.

Physical fitness was defined as “a set of attributes which people have or achieve that relates to the ability to perform physical activity.” (US Department of Health & Human Services 1996, p21). These attributes include cardio-respiratory fitness, muscle strength and muscle power. Physical activity and physical fitness correlate positively with each other (Casperson, Powell and Christenson 1985). The distinction between the two constructs is that fitness is a condition that a person can be in at a point in time and activity is an energy-consuming process (American College of Sports Medicine)

Fatigue was defined as a subjective "feeling of lack of energy, weariness and aversion to effort" (Lewis et al. 2011, p295). This review was interested in chronic fatigue so studies that used a questionnaire that had been specifically developed to measure fatigue or tiredness in daily life were included. Studies were excluded where muscle or exertion fatigue was measured in participants directly after they completed a specific fatigue inducing exercise. Chronic fatigue differs from muscle or exertion fatigue in a number of ways. Chronic fatigue is considered to be a chronic, subjective experience which is often out of proportion to the amount of previous activity (Staub and Bogousslavsky 2001) and is often not resolved by sleep or rest (McGeough et al. 2009). Muscle or exertion fatigue is a more objective fatigue. It is a physiological response to overexertion, is acute in nature and can be ameliorated by rest (Tseng et al. 2010; McGeough et al. 2009).

An observational study was defined as any study where no intervention took place. However papers were included if both post-stroke chronic fatigue and one or more measures of physical fitness and/or physical activity were taken and reported at the baseline of an intervention study.

Results

The original electronic search identified 1291 citations, after Endnote had removed duplicates. Twenty nine full texts were retrieved, of which, three papers, recruiting a total of 444 participants, fulfilled inclusion criteria (Figure 3.1). The updated search retrieved a further five papers, recruiting a total of 234 participants, which fulfilled the inclusion criteria. Scrutiny of reference lists provided no further papers for inclusion. The main reasons for excluding a study were; a) review with no primary data b) fatigue was not measured or c) the type of activity measured did not meet the inclusion criteria, for example measured gait patterns, single limb activity or participants self-reported *ability* to walk in the community (as opposed to quantity of activity).

All eight eligible studies were cross-sectional (Miller et al. 2013; Hoang et al. 2012; Lewis et al. 2011; Robinson et al. 2011; Tseng et al. 2010; Michael and Macko 2007; Michael, Allen and Macko 2006; Shaughnessy, Resnick and Macko 2006) two included only ischaemic strokes (Michael and Macko 2007, Michael, Allen and Macko 2006) and six included both ischaemic and haemorrhagic strokes (Miller et al. 2013; Hoang et al. 2012; Lewis et al. 2011; Robinson et al. 2011; Tseng et al. 2010; Shaughnessy, Resnick and Macko 2006). Mean participant age ranged from 59 years to 71 years. In two studies (Michael and Macko 2007, Michael, Allen and Macko 2006) the participants were all community dwelling and were able to walk with or without a walking aid. In one study (Shaughnessy, Resnick and Macko 2006), participants were either attendees of a National Stroke Association support group or participated in the study by completing a questionnaire online. In one study all participants had been discharged from hospital and were independently ambulatory (Lewis et al. 2011); in another study all participants lived in the community or in an assisted living centre and were able to walk at least 10 feet (Robinson et al. 2011), in one study participants were recruited through local support groups and a participant database and all had the ability to use a total body recumbent stepper machine (Tseng et al. 2010), in one study all participants had completed all inpatient stroke rehabilitation and were recruited from several sources including support group meetings and spasticity clinics (Miller et al. 2013), finally one study included inpatients as well as outpatients (Hoang et al. 2012).

The Fatigue Severity Scale (FSS) was used as the measure of fatigue in six of the studies. Mean FSS scores were reported as 3.9 (Michael, Allen and Macko 2006), 3.28 (Michael and Macko 2007), 4.0 (Robinson et al. 2011), 4.3 (Hoang et al. 2012) and 4.2 (Tseng et al. 2010). Miller et al. (2013) did not report the mean FSS score. An average score of > 4 on the FSS was used as the cut-off for defining fatigue. The percentage of participants categorised with fatigue were 46% (Michael, Allen and Macko 2006), 42% (Michael and Macko 2007), 48% (Robinson et al. 2011), 66% (Hoang et al. 2012) and 66% (Miller et al. 2013). Tseng et al. (2010) did not report the percentage categorised as fatigued. In one study, (Shaughnessy, Resnick and

Macko 2006) 68% either agreed or strongly agreed that fatigue influenced their daily activities. In one study (Lewis et al. 2011), the vitality scale of the SF-36v2 was used to assess fatigue. They reported a mean vitality score of 53.6 but did not specify a cut-off score so did not report percentage of participants who were fatigued.

Table 3.1 - Studies reporting an association between post-stroke fatigue and either physical fitness or physical activity.

Author	Title	Aims and Objectives	Study Design	Time post stroke	Evaluation of fatigue	Measure(s) of physical activity or physical fitness	N	Association between fatigue and physical activity and/or fitness
Michael, Allen & Macko 2006	Fatigue after stroke: relationship to mobility, fitness, ambulatory activity, social support and falls efficacy	"To explore the relationships of fatigue to, cardiovascular fitness, mobility deficit severity, ambulatory activity patterns, social support and self -efficacy for falls"(p211).	Observational, cross sectional	6-166 months (mean 10.3)	Fatigue Severity Scale (FSS) paired with a visual analogue scale (VAS)	Economy of gait, peak exercise capacity (V02 peak), ambulatory activity (steps per 24 hours).	53 (58.5% male)	No significant differences between fatigued and non-fatigued groups in the fitness measures of economy of gait and $\dot{V}O2$ peak and ambulatory activity. Steps per 24 hours in those with fatigue 2696 (SD 1524) Steps per 24 hours in those without fatigue 2751 (SD 1528) Economy of gait with fatigue – 8.8 ml/kg/min (SD 1.67) Economy of gait without fatigue – 8.6 ml/kg/min (SD 1.88) $\dot{V}O2$ Peak with fatigue – 11.34 ml/kg/min (SD 3.04) $\dot{V}O2$ Peak without fatigue – 11.69 ml/kg/min (SD 2.83) When using the FSS as a continuous variable, linear regression showed that economy gait, $\dot{V}O2$ peak and ambulatory activity are not significant predictors of fatigue severity.
Michael & Macko 2007	Ambulatory activity intensity profiles,	"To describe household and community ambulatory	Observational, cross sectional	6-166 months (mean 10.3)	Fatigue Severity Scale (FSS)	Daily step count and intensity of ambulatory activity: Low intensity <16	79 (53% male)	No significant associations between fitness, step activity and fatigue. Correlation between step intensity and

	fitness and fatigue in chronic stroke	activity profiles in terms of step counts & step intensity levels. To determine whether these profiles are related to fitness or self-reported fatigue" (p6).				steps per minute Medium intensity ≥16 and < 30 steps per minute High intensity ≥30 steps per minute. Economy of gait Peak exercise capacity (V̇O2 peak)		fatigue Step Intensity Pearson's r Low 0.093 Medium 0.167 High 0.073
Shaughnessy, Resnick & Macko 2006	Testing a model of post-stroke exercise behavior	To test "a theoretical model of physical activity in stroke survivors" (p15).	Survey cross-sectional by postal and online questionnaire.	60.2 months	Single question: "Does fatigue influence daily activities" with five point likert response scale	Single question "how often do you engage in activity/exercise?" Response options: "never, less than once per week, 1-3 times per week, 4 or more days per week" (p16). Activity/ exercise was defined as "participation in a physical activity of at least 20 minutes duration that caused sweating or increases in respiratory or heart rate" (p16)	312 (41% Male)	No significant association between self - reported exercise behaviour and fatigue. Structural equation modelling techniques showed that fatigue indirectly influenced exercise through self -efficacy expectations.
Miller et	Fatigue and	This study	Observational,	> 6	Fatigue	Six minute walk test	77	No significant correlation between 6MWT,

al. 2013	pain: relationships with physical performance and patient beliefs after stroke	aims to examine "the frequency and impact of fatigue and pain in people with chronic stroke" (p347).	cross-sectional.	months post-stroke. 79.2% were > 12 months post-stroke.	Severity Scale (FSS)	(6MWT) 10-meter walk test (10MWT)	(75.3% male)	10MWT and fatigue. (Significance level was set at 0.008 after Bonferroni correction) Correlation between 6MWT, 10MWT and fatigue 6MWT - r = -0.260, p = 0.023 10MWT - r = -0.175, p = 0.128
Hoang et al. 2012	Physical factors associated with fatigue after stroke: an exploratory study	This study aims "to look for a relationship between physical fatigue and physical parameters in patients at least 3 months post stroke" (p369).	Observational, cross sectional	40 months (42.2)	Fatigue Severity Scale (FSS)	Six minute walk test (6MWT) 10-meter walk test (10MWT)	32 (66% male)	No significant difference between those who were fatigued and those who were not fatigued on 6MWT or 10MWT scores. 6MWT - with fatigue 193.2 meters (111.9), without fatigue 218.3meters (111.1) , p = 0.358. 10MWT - with fatigue 0.6m/s (0.3), without fatigue 0.6m/s (0.3), p = 0.764.
Robinson et al. 2011	Participation in community walking following stroke: subjective versus objective measures and the impact of personal factors	This study aims to examine "the association between subjective and objective measures of participation in community walking and the association between	Observational, cross-sectional.	85 months (89.9)	Fatigue Severity Scale (FSS)	Number of steps taken per day	46 (54% male)	Significant correlation between number of steps taken per day and fatigue. r = -0.380, p< 0.01.

		personal factors and participation in community walking" (p1865).						
Lewis et al. 2011	Is fatigue after stroke associated with physical de-conditioning? A cross-sectional study in ambulatory stroke survivors	"To determine the relationship between a measure of fatigue and 2 indices of physical fitness, lower limb extensor power (LLEP) and walking economy"(p295).	Observational, cross-sectional	160 days (IQR, 84-280 days)	Vitality scale of the SF-36v2.	Walking economy ($\dot{V}O2$) Lower limb Extensor Power (LLEP)	58 (54.4% male)	Walking economy was not significantly related to the vitality scale of SF-36v2. Higher LLEP was signiciantly associated with higher vitality scores (i.e. less fatigue). $r = 0.38$, $p = 0.003$.
Tseng et al. 2010	Exertion fatigue and chronic fatigue are two distinct constructs in people post-stroke.	This study aims "to identify the contributing factors of exertion fatigue and chronic fatigue in people post-stroke" (p2908).	Observational, cross-sectional.	4.1 years (3.5)	Fatigue Severity Scale	Peak exercise capacity $\dot{V}O2$ peak)	21 (57.1% male)	No significant association between chronic fatigue and $\dot{V}O2$ peak. $r = -0.125$, $p > 0.05$.

Association between physical fitness and fatigue

Six studies investigated whether there was an association between physical fitness and fatigue. The aspects of fitness which were assessed were economy of gait (rate of oxygen consumption, $\dot{V}O2$) (Michael and Macko 2007, Michael, Allen and Macko 2006; Lewis et al. 2011), peak exercise capacity ($\dot{V}O2$ peak) (Michael and Macko 2007; Michael, Allen and Macko 2006; Tseng et al. 2010), lower limb extensor power (Lewis et al. 2011), 10 meter walk test (Hoang et al. 2012; Miller et al. 2013) and the six minute walk test (Hoang et al. 2012; Miller et al. 2013). Lewis et al. (2011) reported that higher lower limb extensor power of the leg unaffected by the stroke was significantly associated with less fatigue. All the other studies reported no significant association between fatigue and measures of physical fitness (Table 3.1).

Association between physical activity and fatigue

Four of the included studies explored the relationship between one form of physical activity and fatigue. Two studies measured participant daily step count (Robinson et al. 2011; Michael, Allen and Macko 2006), another study measured the intensity of ambulatory activity by recording the number of steps per minute (Michael and Macko 2007), in a fourth study (Shaughnessy, Resnick and Macko 2006) participants indicated through a single question how many times a week they participated in a physical activity of at least 20 minutes duration that caused sweating or increases in respiratory or heart rate.

Robinson et al. (2011) reported that higher fatigue was significantly associated with lower number of steps taken per day. Shaughnessy, Resnick and Macko (2006) did not find a direct relationship between activity and fatigue but did find, through structural equation modelling techniques that fatigue indirectly influences exercise through self-efficacy expectations.

The other two studies did not find an association between measures of physical activity and fatigue (Table 3.1).

Discussion

This is the first systematic review of studies that has investigated associations between physical fitness, physical activity and post-stroke chronic fatigue. This review found only eight studies which met the inclusion criteria. These studies were cross-sectional, observational studies. Six used the FSS, two used both the FSS and a visual analogue scale, one used the vitality scale of the SF-36v2 and one measured fatigue with a single question with a five point Likert response scale. Physical activity and fitness were measured in different ways.

Only two of these studies found a statistically significant direct relationship between post-stroke fatigue and either physical fitness or physical activity. One study, however, did find that participants with higher levels of fatigue were more likely to have lower self-efficacy expectations for exercise and therefore were less likely to participate in physical activity. Therefore the evidence that this review has provided regarding an association between post-stroke fatigue and either physical activity and/or physical fitness is very limited.

In this respect the stroke literature can be contrasted with the literature on the relationship between fatigue and activity and/or fitness in CFS, MS and cancer patients where significantly more studies have been done in recent years. Indeed, a Cochrane review identified eight trials which investigated physical activity as a treatment for CFS (Larun et al. 2015), another Cochrane review identified as many as 56 trials which investigated the effect of exercise on cancer-related fatigue (Cramp and Byron-Daniel 2013) and a recent review which investigated the effects of exercise training on fatigue in MS patients identified 30 studies (Latimer-Cheung et al. 2013).

Strengths and limitations of this systematic review

The strengths of the review include a thorough search strategy and independent data extraction by two data extractors for the initial search (FD and MK). The limitations are that only papers published in English were included which may have led to the exclusion of relevant studies published in other languages and a methodological screening of the included studies was not carried out.

Limitations of studies included in the review

All eight studies included in this review contained limitations. For example: most included small samples sizes (range n = 21-79); one study only used a single question to measure fatigue (Shaughnessy, Resnick and Macko 2006) and in two studies participants had volunteered themselves for the exercise program (Michael and Macko 2007, Michael, Allen and Macko 2006). In another three studies, participants were excluded if they were unable to walk independently (Hoang et al. 2012; Lewis et al. 2011; Robinson et al. 2011) and the participants in one study showed high levels of physical functioning (Miller et al. 2013) so it may not be possible to generalise the results of these studies to people with more disability. In addition the majority of participants in one study (Shaughnessy, Resnick and Macko 2006) were white, female and unmarried (and so unrepresentative of stroke survivors). Moreover, all studies were cross-sectional which means that it was not possible to identify how the relationships between fatigue and physical activity and/or physical fitness may change over time.

Finally, it should also be taken into consideration that a potential alternative explanation regarding why most of these included studies found no statistically significant associations between fitness and fatigue is that all or most participants in each study may have had similar levels of fatigue and/or similar levels of fitness to each other. The result of such homogenous samples is that significant associations between fitness and fatigue may not be detected even if such associations did exist. Potentially using more sensitive methods of assessing fatigue or measuring fitness would address this problem as doing so would increase the variation of scores on these variables.

Conclusion

In conclusion the systematic review found very limited evidence regarding the relationship between post stroke chronic fatigue and activity and/or fitness. The fact that enough new studies were published in the last few years to warrant this systematic review being updated shows that this area of research is an emerging field but there is still not sufficient evidence to conclude that post stroke fatigue is associated with low levels of activity and/or fitness. However it still remains highly plausible that exercise could be an effective treatment for fatigue after stroke as numerous studies have suggested this in the CFS, MS and cancer literature.

The relationship between fatigue after stroke and reduced physical activity and/or physical fitness will be explored further in Chapter 5 of this thesis.

Summary of Chapter 3

Background and aims

- One hypothesis is that chronic fatigue after stroke might be triggered by physical de-conditioning which sets up a vicious, self-perpetuating cycle of fatigue, avoidance of physical activity, further de-conditioning and more fatigue. If an association between physical activity and fatigue after stroke could be established this would provide a rationale for developing a physical activity based treatment.

- This chapter aimed to systematically review all observational studies which have measured both fatigue post stroke *and* one or more measures of physical fitness and/or physical activity at the same time point and reported the association between fatigue and fitness variables.

Method

- Publications were identified by systematically searching databases MEDLINE, EMBASE, CINAHL, PsycInfo and Sportdiscus using keywords “fatigue”, “stroke”, “fitness” or “activity” and their associated terms or synonyms. Publications that provided data on associations between fatigue in stroke patients and levels of physical activity, cardio-respiratory fitness and/or muscle strength and mass were included.

Results

- Eight studies fulfilled the inclusion criteria. Only two of these studies found a statistically significant relationship between post-stroke fatigue and either physical activity and/or physical fitness. One study did find, through structural equation modelling techniques that fatigue indirectly influences exercise through self-efficacy expectations.

Conclusions

- The current evidence regarding associations between exercise, fitness and fatigue after stroke is very limited.

Chapter 4 – Longitudinal Cohort Study of Fatigue After Stroke: Its Frequency and Natural History.

Data from this chapter have been published in the Journal of Psychosomatic Research (Duncan et al. 2014). The full paper has been included as a Appendix (Appendix 9).

Contributions to the study

The study was designed by Professor Gillian Mead with help from Professor Martin Dennis, Professor Alasdair MacLullich, Dr Susan Lewis, Dr Carolyn Greig and Professor Michael Sharpe.

The PhD candidate:

- recruited all participants except for three who were very kindly recruited by Dr Mansur Kutbaev.
- collected all data at time of recruitment by administering questionnaires, the MMSE and NIHSS as well as directly from patients' medical notes
- obtained informed consent
- arranged and carried out all follow-up assessments i.e. collected all data.
- entered all data into SPSS database
- carried out the majority of the statistical analysis in this Chapter under the advisement of Dr Susan Lewis.

This work was supported by the Chief Scientist Office of the Scottish Government.

Abstract

Objective: Fatigue is often distressing for stroke survivors. The time course of clinically significant fatigue in the first year after stroke is uncertain. This study aimed to determine the frequency, severity and time course of clinically significant fatigue in the first 12 months after stroke onset.

Methods: Patients with a recent acute stroke were recruited. At one month, six months and 12 months, a structured interview to identify clinically significant fatigue (case definition) was performed, and participants filled out a questionnaire which assessed fatigue severity (Fatigue Assessment Scale (FAS)).

Results: Of 157 patients who initially consented, 136 attended at least one assessment. At one month, 43/132 (33%) had clinically significant fatigue. Eighty-six attended all three assessments, of whom clinically significant fatigue was present in 24 (28%) at one month, 20 (23%) at six months and 18 (21%) at 12 months; their median (IQR) FAS scores were 23 (18 to 29), 21 (17 to 25) and 22.5 (17 to 28) at one, six and 12 months respectively. Of 101 patients who attended at least the one and six month assessments, fatigue status did not change in 65 (64%), with 9 (9%) fatigued throughout and 56 (55%) non-fatigued throughout; 15 (15%) became non-fatigued, 9 (9%) became fatigued, and in 12 (12%) fatigue status fluctuated across three assessments.

Conclusion: Clinically significant fatigue affected a third of patients one month after stroke. About two thirds of these patients had become non-fatigued by six months, most of whom remained non-fatigued at 12 months.

Rationale

The systematic review in Chapter 2 identified nine longitudinal studies which investigated the frequency and natural history of post-stroke fatigue. All of these studies determined the presence or absence of fatigue by using a cut-off score on a multi-item scale, a single item on a larger scale or a single question. Arguably these methods result in the presence of fatigue being determined arbitrarily instead of in a meaningful way. In other words these methods do not establish whether the fatigue is clinically significant i.e. does the fatigue actually matter to the stroke survivor and therefore warrant treatment.

Using a case definition for clinically significant fatigue would be a more valuable method of assessing the frequency and natural history of post-stroke fatigue as using this method would allow researchers to find out how many stroke survivors actually consider their fatigue to be problematic and may wish to seek out an intervention. If such a case definition were to be used in a longitudinal study then it could be determined whether the frequency of problematic fatigue changes over time. This information could be used by researchers and clinicians to advise patients about whether their fatigue is likely to remain troublesome. This information could also be used to assess whether there is a need for an intervention to be developed. The systematic review in Chapter 2 confirmed that there are no previous longitudinal cohort studies that have used a case definition approach to identifying post-stroke fatigue and the one longitudinal study published since the systematic review search was carried out on 7th April 2011 also did not use a case definition approach.

The aims of this longitudinal cohort study were therefore to:

a) investigate the frequency and natural history of clinically significant fatigue over the first year, as defined by a case definition for post-stroke fatigue (Lynch et al. 2007) for cohort of stroke patients as a whole.

b) investigate the natural history of clinically significant fatigue as defined by a case definition for each *individual* participant.

c) investigate how the case definition for post-stroke fatigue relates to a continuous multi-item scale for assessing fatigue severity (Fatigue Assessment Scale (FAS) (Michielsen et al. 2001).

Method

Design

The design of the study was a prospective longitudinal cohort study of stroke patients. Baseline information was collected at recruitment and follow-up assessments took place at one, six and 12 months after stroke onset. (This study was initially designed by Professor Gillian Mead, Professor Martin Dennis, Dr Susan Lewis, Dr Carolyn Greig, Professor Alastair MacLullich and Professor Michael Sharpe).

Ethical Approval

Approval from Lothian Research Ethics Committee was obtained (Appendix 22) and all participants gave written informed consent.

Participants

The initial aim was to recruit 170 stroke patients over an 18 month period starting from September 2009. The target of 170 was chosen as it was anticipated that approximately 350 eligible patients would be seen in the inpatient and outpatient services in Edinburgh during the time frame of the study and it was anticipated that it would be feasible to recruit half of these patients. At the beginning of the study, it was assumed that 120 people out of these 170 would attend all three assessments and it was calculated that for n = 120, and a frequency of clinically significant fatigue of 36% (based on Lynch 2007), the 95% Confidence Interval would be 27% to 45%. (This power calculation was made by Dr Susan Lewis).

Participants were recruited from:

- Two acute stroke units - Edinburgh Royal Infirmary and Western General Hospital
- A combined acute assessment ward. This is where suspected stroke patients are assessed by specialist staff and depending on the results of initial clinical tests may be either discharged home or admitted to the stroke unit (NHS Lothian, The Royal Infirmary of Edinburgh, Combined Assessment).
- A neurovascular outpatient clinic - based at the Western General Hospital

- Three rehabilitation hospitals in Edinburgh: The Astley Ainslie Hospital, Liberton Hospital, The Royal Victoria Hospital.

Due to a lower than anticipated recruitment rate the period for recruitment was extended by four months and ended on 30th June 2011. Recruitment was initially limited to patients who were registered with GP practices in East Lothian and South Edinburgh to ensure that this study was as close to a community based study as possible (the main railway line being the divide between north and south Edinburgh). After 14th July 2010 this catchment area was expanded slightly so that it also included an additional nine GP practices that are situated just north of the railway line.

Inpatients

Inpatients were identified as suitable by liaising with nursing staff or by examining medical notes and were approached directly by the researcher (FD) on the ward as soon after admission as possible. The requirements of the study were explained and patients were given an information sheet to read (Appendix 10). The researcher returned later to ask if they wished to participate. The patient was asked to sign a consent form (Appendix 11) if they wished to participate. The stroke unit at Edinburgh Royal Infirmary was visited daily (Monday - Friday) by the researcher. The researcher did not visit the ward at the weekends. Consequently any stroke patient who was admitted after 5pm on the Friday and discharged before Monday was not approached regarding participating in the study.

Outpatients

Outpatients were identified by the researcher attending two outpatient clinics a week and placing a letter on the notes of patients in the study catchment area. The letter asked the clinic's physicians to hand out the study information sheet to patients who had probably or definitely had a stroke. If the patient indicated that they were interested in taking part in the study, the physician would give their details to the researcher who, after at least 24 hours, would recruit the patient to the study by telephone call.

Patients who were more than one month from stroke onset were not recruited to the study as such patients would have been too late for the one month follow-up assessment.

Patients were not recruited to the study if they did not have the mental capacity to understand the requirements of the study or to consent to taking part.

Patients with dysphasia

An "aphasia friendly" information sheet and consent form was produced by Speech and Language Therapist Professor Marian Brady. These materials were given to potential participants who had mild dysphasia at the time of recruitment.

Inclusion and Exclusion Criteria

All strokes (ischaemic and haemorrhagic, first and recurrent) were included. Patients diagnosed with a Transient Ischaemic Attack (T.I.A.) or subarachnoid haemorrhage (unless secondary to an intraparenchymal haemorrhage) were excluded. Patients were excluded from the study if they had confusion, dementia or reduced consciousness level severe enough that they were unable to understand the rationale of the study and therefore unable to give informed consent, if they scored less than 20 on the Mini-Mental State Examination (MMSE) or if they were medically unstable. Dysphasic patients (either receptive or expressive) were also excluded unless their dysphasia was very mild. Patients who could not consent at time of stroke were re-evaluated again within one month and if sufficiently improved were included. Patients who could not speak English or were under the age of 18 were also excluded.

Measurements

Baseline Data

At the time of recruitment, the researcher collected data directly from the participants using the following instruments:

The National Institute of Health Stroke Severity Scale (NIHSS) (National Institute of Health) is a 15-item measure of stroke severity. Training for the NIHSS was provided by an online course which the researcher completed. The researcher observed the patient's ability to answer questions and perform activities that are designed to assess level of consciousness, gaze, visual field loss, facial palsy, motor strength, ataxia, sensory loss, language, dysarthria and neglect. Each item on the scale is scored with a higher score indicating a more severe stroke.

The Mini-Mental State Examination (MMSE) (Folstein, Folstein and Fanjiang 2001) is a tool for screening for cognitive impairment. The researcher noted the patient's performance across ten items which test different cognitive abilities with a total possible score of 30. Scores of 27-30 are considered normal, 21-26 as mild, 11-20 as moderate and 10 or less as severe cognitive impairment (Poynter, Kwan and Vassallo 2013). Patients were not recruited to the study if they scored less than 20 on this test or if there were any doubts amongst clinical staff or the researcher regarding the patient's ability for informed consent.

Participants were asked the question, requiring a YES/ NO response; "Did you have a problem with fatigue before your stroke?" (Lynch et al. 2007).

Inpatients completed these measures in the hospital at the time of consent. Patients recruited from the outpatient clinic completed most of these measures at the same time as their one month follow up. The NIHSS score for the outpatients was calculated at a later date from each patient's medical records by a neurologist (MK). It has been reported that NIHSS scores can be taken from medical records with a good level of reliability and validity (Kasner et al. 1999).

Information was also extracted from medical records regarding whether the participant's stroke was ischaemic or haemorrhagic, whether the lesion was on the left or right side of the brain or whether it was bilateral and whether the stroke's subtype according to Oxfordshire Community Stroke Project Classification was a Lacunar stroke (LACS), a Partial anterior circulation stroke (PACS), a Posterior circulation stroke (POCS), or a Total anterior circulation stroke (TACS) (Bamford et al. 1991). These classifications were checked by a neurologist (MK). It was also noted whether participants had a history of hypertension or diabetes and what their blood pressure was on admission to hospital or at time of outpatient appointment.

A social deprivation rank for each participant was ascertained by using the Scottish Index of Multiple Deprivation (The Scottish Government). This index allocates each postcode in Scotland to a relative deprivation rank. The index consists of 6505 different ranks. Rank one being the most deprived and rank 6505 being the least deprived. The factors which are taken into account when calculating ranks and their weightings are current income (28%), employment (28%), health (14%), education (14%), geographic access (9%), crime (5%) and housing (2%). In this study the participant's postcodes at time of recruitment according to their hospital records were used.

Follow-up Assessments

Each participant was invited to attend three follow-up assessments scheduled to take place one, six and 12 months after stroke onset.

Follow-up assessments were carried out at the Clinical Research Facility based at the Royal Infirmary, Edinburgh. Participants who were inpatients at one of the rehabilitation hospitals at the time of follow-up were assessed on their ward. Participants were offered free transport by taxi cab, however some participants were unable or unwilling to travel to the Royal Infirmary and they were assessed in their own home.

The researcher collected data directly from the participants at follow-up assessments using the following instruments and questionnaires.

Fatigue

Fatigue was assessed using two instruments; the Fatigue Case Definition (to assess clinically significant or problematic fatigue) and the Fatigue Assessment Scale (FAS) (to assess fatigue severity).

Fatigue Case Definition

A case definition for post-stroke fatigue and an associated structured interview was developed by Lynch et al. (2007). The interview consisted of seven questions designed to encourage participants to talk about how they have been feeling in the past month. The interviewer must ascertain from the responses to these questions whether the participant had experienced:

- "fatigue, a lack of energy or an increased need to rest every day or nearly every day" for at least a two week period in the past month (Lynch et al. 2007, p543).
- "fatigue or a lack of energy as opposed to sleepiness, lack of motivation or boredom" (Lynch et al. 2007, p544).
- fatigue which was present for more than 50 per cent of the day (the researcher did not specify to the participant whether this question referred to all of the day or just to waking hours).
- fatigue which has interfered with their ability to take part in everyday activities and/or is a problem for them.

The interviewer can ask as many further probe questions as necessary if any of the participant's responses need further clarification.

If the participant indicated that they had experienced fatigue, that was not sleepiness, lack of motivation or boredom, every day or nearly every day and that their fatigue lasted more than 50 per cent of the day and was a problem for them then they fulfilled the case definition and were considered to have clinically significant fatigue.

If the participant responded "no" to the first question "Have you felt tired over the last month?" the interviewer skipped the probe questions which explored the nature of this fatigue and asked the final question "Do you feel that fatigue is a problem for you?"

The Fatigue Assessment Scale

The Fatigue Assessment Scale (Michielsen et al. 2001) is a self-report measure which requires participants to respond to ten statements about different aspects of fatigue by choosing one of five answer categories (1 = never, 2 = sometimes, 3 = regularly, 4 = often, 5 = always) The scores are then summed to obtain a total fatigue score.   The decision to use the FAS as opposed to other methods of assessing fatigue severity was informed by a previous study which compared the feasibility and reliability of four fatigue scales in stroke patients and reported that in terms of feasibility and reliability, the FAS was the best overall choice (Mead 2007).

The FAS was used in addition to the case definition for clinically significant fatigue so that the case definition results could be put in the context of a fatigue severity scale. This will enable information about the relationship between case definition fulfilment and fatigue severity to be ascertained.

Suitability of the measures

The study which originally constructed the fatigue case definition (Lynch et al. 2007) reported it to be feasible to administer with stroke patients as all participants provided satisfactory answers to all the probe questions, that it had good test-retest reliability between the first case definition interview and a second one carried out four days later, that it had very good inter-rater reliability and finally that it had good concurrent validity as participants who fulfilled the case definition generally had much higher fatigue scores on four fatigue scales than participants who did not fulfil the case definition.

The feasibility of using the FAS in stroke patients has been demonstrated in Mead et al. (2007) which reported that all of 55 participants completed all questions except three patients who missed one question each. The FAS has been reported to have acceptable internal consistency (Smith et al. 2008) and good test-retest reliability (Smith et al. 2008; Mead et al. 2007) in a stroke population. The FAS has also been reported to have moderate to high convergent construct validity with another two fatigue scales (POMS-fatigue and MFSI general) which were completed by the same stroke patients (Mead et al. 2007). Finally, the FAS has been reported to have good divergent validity in stroke patients because it was found to measure fatigue and not depression (Smith et al. 2008).

Preparing Data for Analysis

All data were initially recorded on paper data collection forms. A database was created in SPSS 14.0 and then 19.0 for Windows to which all data were entered.

Data checking

After the data were entered, every data point except the activity data (discussed in Chapter 5) were manually checked against the paper data recording sheets by FD to ensure no data entry errors had been made. (Activity data were checked by Dr Susan Lewis). All continuous variables were checked for outlying values by creating boxplots in SPSS. The reasons for these outliers were identified if possible and noted. Outlying values were not removed or altered unless they were a data entry mistake or a measurement error such as an instrument failure. An exception to this is where the value is correct but by checking we find there is something special about that individual i.e. a low score on the muscle strength measure being due to the participant having an artificial leg.

Procedure for dealing with missing values in the data set.

The dataset contained missing values for three main reasons:

- A participant did not attend an assessment
- A participant may have refused or been physically unable to take part in a particular test (Note: this scenario is relevant to tests not described until Chapter 5).
- A participant did not answer one or more questions on a questionnaire because they did not understand it, could not relate to it or because they simply accidentally missed it out and the missing value was not picked up by the researcher at the time.

The vast majority of missing values in the dataset were not replaced except on the occasions when a self-report questionnaire was not fully completed. In these cases the missing value was replaced with the median of the participant’s other answers on the questionnaire in which the missing value occurred (IBM Knowledge Center). Only a small number of answers were missed on the FAS questionnaires at each of the three time points. Appendix 12 shows the number of answers that were missed for each questionnaire.

Sensitivity analyses – All relevant analyses were performed with missing values replaced and without missing values replaced to see what effect this had on the results.

Missing data due to participants being lost to follow-up.

Missing data due to participants being lost to follow-up was dealt with by presenting the median FAS scores and frequency of case definition fulfilment at each time point for just those participants who attended all three assessments. This is called the Complete Case Analysis or Listwise Deletion approach to dealing with missing data.

The Complete Case Analysis or Listwise Deletion approach to dealing with missing data is the most commonly used approach in longitudinal studies (Nakai and Ke 2011; Enders 2010) and the approach which has been used in previous longitudinal studies of fatigue after stroke (Duncan, Wu and Mead 2012). The advantages of using this approach are that results can be directly compared across all three time points which means more accurate information about any changes regarding important variables is obtained. One disadvantage of this approach is that if some participants were lost to follow-up because of fatigue or illness then the participants left in the analysis may not be representative of all participants. In other words, this approach may lead to a healthy survivor bias. Another disadvantage of this approach is that excluding too many cases may reduce the power and therefore the precision of the estimate to unacceptable levels.

Therefore to address the disadvantages of the complete case analysis approach the results for the whole cohort of participants are presented as well as the results for the participants who attended all three assessments.

Normality Checks

Before any inferential statistical tests were performed all variables in the dataset that were measured at least at interval level (i.e. not categorical or ordinal data) were checked for normality so that it could be determined whether parametric or non-parametric statistical tests were required or whether a data transformation was necessary. This was carried out by creating a histogram for each variable in SPSS, examining characteristics of the distribution such as mean, standard deviation, median, variance, range, skewness and kurtosis and by performing statistical tests designed to determine the normality of a distribution (Kolmogorov-Smirnov test and Shapiro-Wilk test).

Statistical Analysis

Guidance and advice on the statistical analysis was provided by Dr Susan Lewis.

Frequency and natural history of fatigue

The proportion with clinically significant fatigue and 95% confidence intervals at each time point were calculated.

The percentages of participants who answered "yes" to each of the case definition's seven probe questions were calculated.

The median and interquartile range of FAS scores at each time point was determined. A Wilcoxon Signed Rank tests was used to determine whether the difference in FAS scores was significant across time points.

Patterns of clinically significant fatigue over time were explored by examining whether the fatigue status of each individual changes over time according to the case definition. The percentage of participants who were fatigued at all time points, fatigued at no time points or had a fluctuating pattern of fatigue over time were reported.

Additional Analysis

The following further exploratory analyses which were not in the original data plan were carried out:

- to investigate whether there was a relationship between fatigue status as assessed by the case definition and FAS scores.

- to investigate whether participants who were fatigued were more likely to drop-out of the study than participants who were not. It was felt that it was important to perform this additional analysis because if attrition from the study had been selective as opposed to random, then there would be a possibility that the frequency of fatigue at later time points may have been underestimated.

Relationship between fatigue status as assessed by case definition and FAS scores

A Mann-Whitney U test was used to determine if the difference in median FAS scores between those who fulfilled the case definition at each time point and those who did not fulfil the case definition was significant.

A descriptive approach was taken to examine the pattern of fatigue status as assessed by the case definition across two time points in relation to increases or decreases in FAS score over time for each individual.

Selective Attrition

The fatigue results of participants who attended the one and six month follow-up assessments were compared with those who did not attend subsequent assessments using Chi-square and Mann-Whitney U statistical tests.

Service User Group

A service user group consisting of stroke survivors and carers was convened to help guide this longitudinal cohort study.

The group were recruited via the Stroke Research Network and originally 22 stroke survivors and carers reported that they would be interested in taking part in the study. It was planned from the start of the study that four service user group meetings would be organised over the course of the study. These meetings consisted of a presentation of the aims of the study and the progress that had been made to date. The group were then split into smaller groups where they were encouraged to openly discuss their opinions on several aspects of the study. These discussion groups were facilitated by FD and GM. Topics that the group were asked to discuss included how to increase the recruitment rate, how to retain participants in the study, clarity of the participant information sheet or how to inform the participants of the results.

Service user group meetings took place during October 2009, June 2010, September 2011 and June 2012 and were attended by between five and 12 service users. A summary of the group member's comments and the action points taken by the researchers can be found in Appendix 13.

Results

Participants

One hundred and sixty one people agreed to take part in the study. One hundred and forty eight were recruited as inpatients (Figure 4.1) and 13 were recruited from the outpatient clinic (Figure 4.2). Participants were recruited to the study a median of 5 days (IQR 3-8 days; range 0-30 days) after stroke onset.

Figure 4.1 – Inpatient Recruitment

Inpatient Recruitment

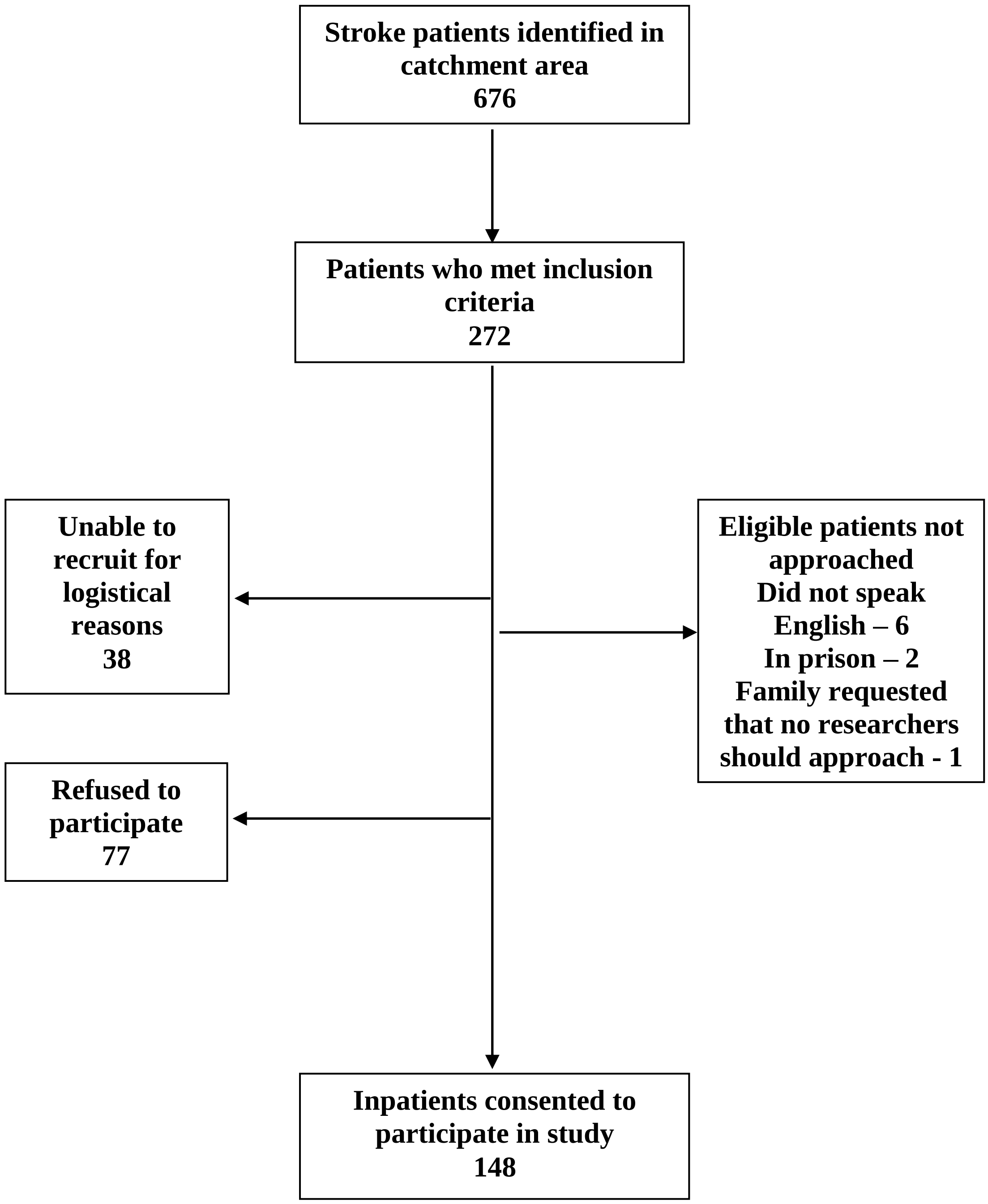
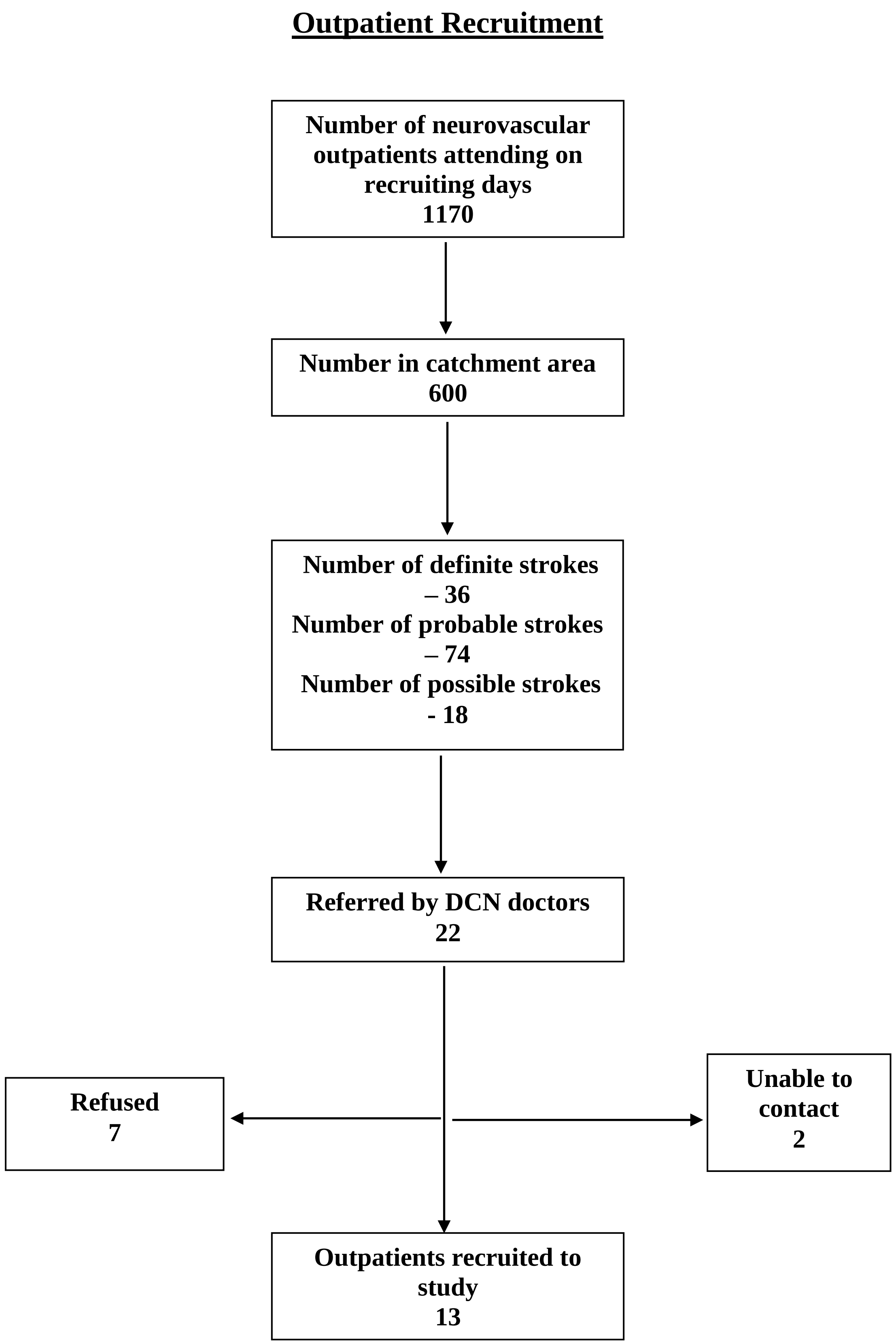


Figure 4.2 – Outpatient recruitment



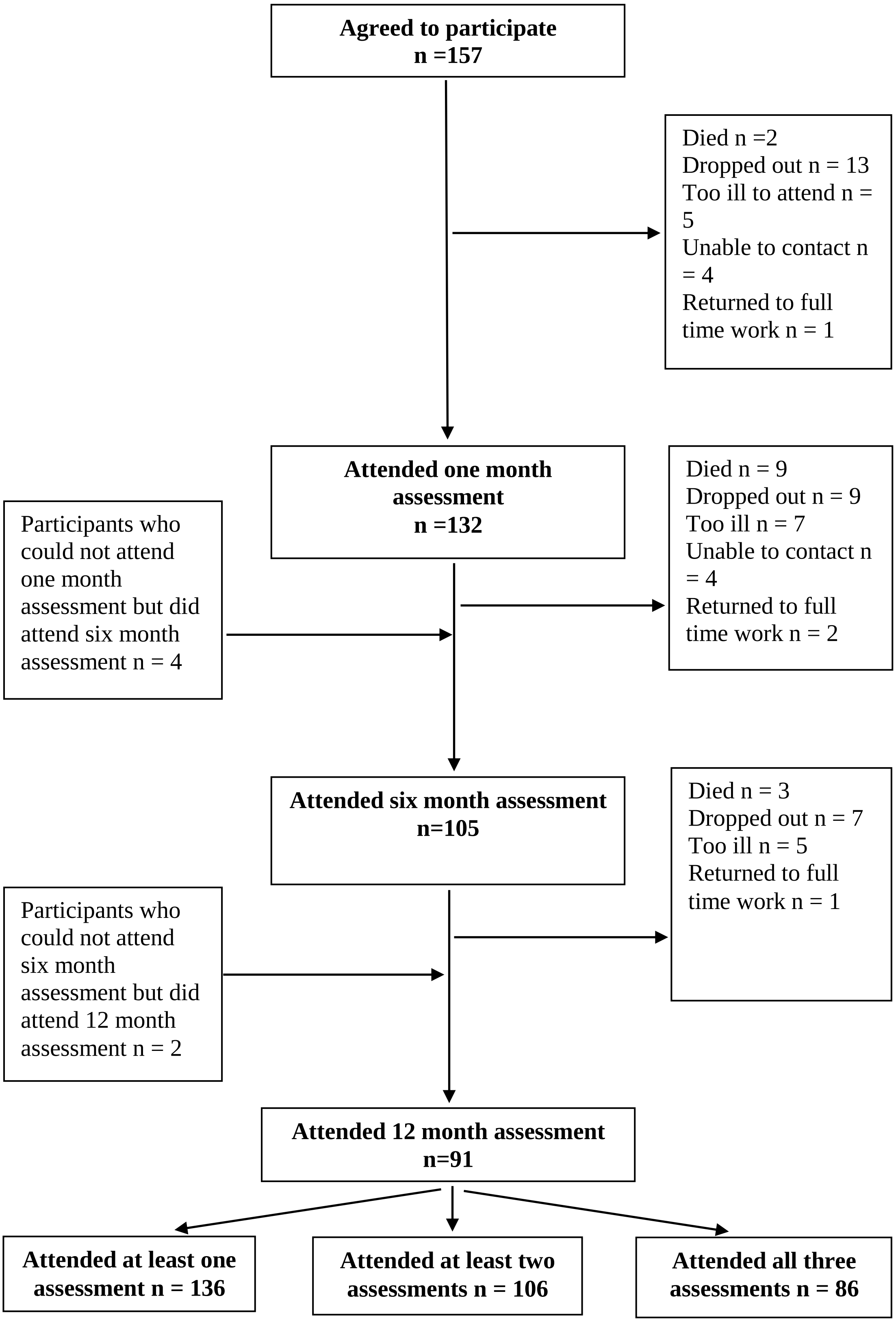
After recruitment it was discovered that four participants had not had a stroke (three were diagnosed with a TIA on discharge and one was diagnosed with another condition 3 weeks after discharge) leaving a total of 157 eligible study participants.

The one, six and 12 month follow-up assessments were attended by 132 (84.1%), 105 (66.9%) and 91 (57.9%) participants respectively out of the 157 stroke patients who agreed to take part. Eighty six participants (54.7%) attended all three assessments. One hundred and one participants (64.3%) attended at least the one and six month assessments.

Fifteen participants (9.5%) attended only the one and six month assessments. Three participants (1.9%) attended only the six and 12 month assessments. One participant (0.6%) attended only the six month assessment and two participants (1.3%) attended only the one and 12 month assessments. One hundred and thirty six participants (86.6%) attended at least one assessment and 106 participants (67.5%) attended at least two assessments.

The reasons why participants were unable to continue with the study are presented in Figure 4.3.

Figure 4.3 - Attrition Flow Diagram



Demographics and Baseline Data

The demographics and baseline data for the 86 participants who attended all three assessments were compared with the data for the 71 participants who did not attend all three assessments (i.e. attended no assessments or only attended one or two assessments). The participants who attended all three assessments were significantly more likely to report having a problem with fatigue before their stroke (p = 0.013) and had a significantly higher MMSE score at recruitment (p = 0.036) than participants who were unable to attend at least one assessment (Table 4.1).

Table 4.1 – Demographics of participants initially recruited, participants who attended all three assessments and of participants who originally consented to take part but were unable to attend all three assessments.

Characteristics at recruitment	**Participants who attended all three assessments (n=86)**	**Participants who originally consented to take part but did not attend all three assessments (i.e. dropped out, died, illness) (N =71)**	**P-value**
Median age, years (IQR)	71.8 (63.5-79.8)	72.2 (58.6-78.8)	0.430[a]
Male (%)	53 (61.6)	46 (64.8)	0.741[b]
First ever stroke (%)	65 (75.6)	58 (81.7)	0.437[b]
Inpatient (%)	78 (90.7)	66 (93)	0.773[b]
Ischaemic stroke (%)	80 (93.0)	67 (94.4)	1.000[b]
Side of brain lesion:			
Left hemisphere (%)	38 (44.2)	24 (33.8)	
Right hemishere (%)	37 (43.0)	39 (54.9)	
Unknown (%)	11 (12.8)	5 (7.0)	
Bilateral (%)	0 (0)	3 (4.2)	0.069[c]

Stroke classification: TACS (%) PACS (%) LACS (%) POCS (%)	 3 (3.5) 34 (39.5) 26 (3.2) 23 (26.7)	 5 (7.0) 33 (46.5) 18 (25.4) 15 (21.1)	 0.524[c]
Answered 'yes' to the question 'Did you have a problem with fatigue before your stroke?' (%)	41 (47.7)	19 (26.8)	**0.013[b]**
History of diabetes (%)	15 (17.4)	11 (15.5)	0.831[b]
History of hypertension (%)	44 (51.2)	36 (50.7)	1.000[b]
Median MMSE (IQR)	28 (25 to 29)	26 (24 to 28)	**0.036[a]**
Median NIHSS (IQR)	2 (1 to 3.75)	3 (2 to 4)	0.096[a]
Mean (SD) Systolic BP at admission	148.2 (26.4)	146.6 (24.6)	0.720[d]
Mean (SD) Diastolic BP at admission	78.9 (14.2)	80.2 (15.5)	0.598[d]

TACS=total anterior circulation syndrome, PACS=partial anterior circulation syndrome, LACS=lacunar syndrome, POCS=posterior circulation syndrome
a = Mann-Whitney U test
b = Fisher’s Exact (2 sided) test
c = Pearson’s Chi-Square
d = T-test
Bold type = $p<0.05$.

Location of Follow-up Assessments

Just over half of all assessments at each time point took place at the Clinical Research Facility. The other assessments took place either in a rehabilitation hospital, a care home or the participant's own home. (Table 4.2)

Table 4.2 – Number of participants who were followed-up at each location.

Location of Assessment	**One Month**	**Six Month**	**12 Month**
Clinical Research Facility	69 (52.3%)	55 (52.4%)	46 (50.5%)
Rehabilitation Hospital (Liberton, Astley Ainslie, Royal Victoria)	32 (24.2%)	0 (0%)	0 (0%)
Home Visit	31 (23.5%)	49 (46.7%)	44 (48.3%)
Care Home	0 (0%)	1 (0.9%)	1 (1.1%)
Total	**132**	**105**	**91**

Assessments carried out at the Clinical Research Facility in the Royal Infirmary took between approximately one hour fifteen minutes and two hours to perform. Assessments carried out in the participant's home or in a rehabilitation hospital took between approximately half an hour and an hour and a half to perform.

Frequency of fatigue after stroke

Clinically significant fatigue (according to the case definition) was present at one, six and 12 months after stroke onset in 43/132 (32.6%), 23/105 (21.9%) and 18/91 (19.8%) of the entire cohort of participants respectively (Table 4.3). Of those participants who attended all three assessments, clinically significant fatigue was present in 24/86 (27.9%), 20/86 (23.3%) and 18/86 (20.9%) respectively (Table 4.4). Of those participants who attended all three assessments, the median FAS score was significantly higher (indicating more severe fatigue) in those attending the one month assessment than in those attending the six month assessment (Wilcoxon Signed Rank test, p=0.025). There was no significant difference between the median FAS score at six months and the median FAS score at 12 months (Wilcoxon Signed Rank test, p = 0.19).

Table 4.3 – Percentage of participants in the whole cohort to fulfil fatigue case definition and median fatigue assessment scale scores at each time point.

	One month (n = 132)	Six months (n = 105)	12 months (n = 91)
Percentage fatigued (95% C.I.)	32.6 (24.6-40.6)	21.9 (14-29.8)	19.8 (11.6-28)
Median FAS Score (IQR)	23 (18-29)	21 (17-25.5)	22 (17-28)

Table 4.4 – Percentage of participants who attended all three assessments to fulfil case definition and median fatigue assessment scale scores at each time point.

	One month (n = 86)	Six months (n = 86)	12 months (n = 86)
Percentage fatigued (95% C.I.)	27.9 (18.4-37.4)	23.3 (14.4-32.2)	20.9 (12.3-29.5)
Median FAS Score (IQR)	23 (18-29)	21 (17-25.25)	22.5 (17-28)

The participant's answers to the seven questions of the fatigue case definition were examined in order to gain further insight into which case definition questions were the most sensitive to the passage of time. (Tables 4.5 - 4.8).

This analysis reveals that the main reasons why fewer participants reported clinically significant fatigue at later time points are that (of the participants who answered "Yes" to question 1a "Have you felt tired over the last month") fewer participants felt tired for more than 50% of the day or considered their tiredness to be a problem for them as time went on.

Table 4.5 – Percentage of participants in the whole cohort who answered “yes” to each fatigue case definition question.

Fatigue case definition individual questions	One Month N= 132	Six Months N=105	12 months N=91
1a. Have you felt tired over the last month?	108 81.8%	75 71.4%	69 75.8%
2a. Do you feel that fatigue is a problem for you?	62 47%	41 39%	31 34.1%

Table 4.6 – Percentage of participants in the whole cohort who answered “yes” to each fatigue case definition question (after excluding those who answered “no” to question 1a).

Fatigue case definition individual questions	One month N = 108	Six months N = 75	12 months N = 69
1bi. Is the tiredness a lack of energy rather than a lack of motivation or boredom?	94 87%	68 90.7%	59 85.5%
1bii Is it a lack of energy rather than a sleepy feeling?	90 83.3%	62 82.7%	56 81.2%
1ci Are you tired every day or nearly every day?	82 75.9%	51 68%	49 71.0%
1cii Are you tired for more than 50% of the day?	61 56.5%	33 44%	24 34.8%
2a. Do you feel that fatigue is a problem for you?	62 57.4%	41 54.7%	31 44.9%

Table 4.7 – Percentage of participants who attended all three assessments who answered “yes” to each fatigue case definition question.

Fatigue case definition individual questions	One Month N= 86	Six Months N= 86	12 months N= 86
1a. Have you felt tired over the last month?	73 84.9%	64 74.4%	65 75.6%
2a. Do you feel that fatigue is a problem for you?	40 46.5%	36 41.9%	31 36.0%

Table 4.8 – Percentage of participants who attended all three assessments who answered "yes" to each fatigue case definition question (after excluding those who answered "no" to question 1a).

Fatigue case definition individual questions	One month N = 73	Six months N = 64	12 months N = 65
1bi. Is the tiredness a lack of energy rather than a lack of motivation or boredom?	62 84.9%	58 90.6%	56 86.1%
1bii Is it a lack of energy rather than a sleepy feeling?	62 84.9%	53 82.8%	53 81.5%
1ci Are you tired every day or nearly every day?	54 73.9%	43 67.2%	48 73.8%
1cii Are you tired for more than 50% of the day?	35 47.9%	29 45.3%	24 36.9%
2a. Do you feel that fatigue is a problem for you?	40 54.8%	36 56.2%	31 47.7%

Note that case definition fulfilment requires that patients response 'yes' to 1a, that the fatigue is a lack of energy, and that the response is 'yes' to items 1ci, 1cii and 2a.

Course of fatigue across time points for individual participants

The analysis of individual patterns of fatigue (according to case definition) revealed that of the participants who attended all three assessments (n=86), 45 (52.3%) participants were not fatigued at any time point, seven (8.1%) had fatigue at all three time points, and 34 (39.5%) had a variable course of fatigue (Table 4.9). Further analysis of individual patterns of fatigue across the 86 who attended all three assessments revealed that of the 24 participants who were fatigued at one month, 16 (66.6%) were not fatigued at six months and 14 (58.3%) were not fatigued at 12 months.

Table 4.9 – Course of fatigue (case definition) across the three time points, for the 86 patients who remained in the study for its entire course.

	Number (%) (n=86)
Fatigued at all three time points	7 (8.1%)
Not fatigued across all three time points	45 (52.3%)
Fatigued at one month but not fatigued	
- by 6 months	13 (15.1%)
- by 12 months	1 (1.2%)
Not fatigued at one month but developed fatigue	
- by 6 months	3 (3.5%)
- by 12 months	5 (5.8%)
Fatigued at one month, not fatigued at six months, fatigued again at 12 months	3 (3.5%)
Not fatigued at one month, fatigued at six months, not fatigued at 12 months	9 (10.5%)

The analysis of individual patterns of fatigue also revealed that of the participants who attended the one and six month assessments but not the 12 month assessment (n=15), two (13.3%) were fatigued at both time points, 11(73.3%) were not fatigued at either time point and two (13.4%) were fatigued at one point but not the other (Table 4.10).

Table 4.10 – Course of fatigue (case definition) across time points, for the 15 patients who attended just the one and six month assessments but not the 12 month assessment.

	Number (%) (n=15)
Fatigued at both time points	2 (13.3%)
Not fatigued at either time point	11 (73.3%)
Fatigued at one month but not fatigued	
- by 6 months	1 (6.7%)
Not fatigued at one month but developed fatigue	
- by 6 months	1 (6.7%)

Additional Analyses

Relationship between clinically significant fatigue (case definition) and fatigue severity (FAS score).

Participants who were fatigued as assessed by the case definition had significantly higher FAS scores than participants who were not fatigued according to the case definition ($p < 0.0001$). This was the case at all three time points (Table 4.11).

(Appendix 14 presents the case definition results and FAS scores for each individual participant).

Table 4.11 – Median FAS scores for those who fulfilled case definition compared to those who did not fulfil case definition at each time point.

Fatigued (as assessed by case definition)	**One Month Median FAS Score (IQR)**	**Six Months Median FAS Score (IQR)**	**12 Months Median FAS Score (IQR)**
Yes	29 (24-33)	28 (22-38)	29 (24.75-38.25)
No	21 (16.5-25.5)	19 (16-24)	20 (15-25)
p-value (Mann-Whitney U test)	< 0.0001	< 0.0001	< 0.0001

Changes in FAS scores in relation to changes in fatigue status according to case definition for individual participants

The course of fatigue across each combination of two time points for each individual participant was examined. A pattern emerged regarding FAS scores of participants who were fatigued according to case definition at one time point but not the other.

FAS scores increased between one and six months in 53.8% of participants who were not fatigued at one month but then developed fatigue at six months according to the case definition. Similarly, FAS scores increased in 75% of participants who were not fatigued at one month but then developed it by 12 months according to the case definition and FAS scores increased in 100% of participants who were not fatigued at six months but then developed it by 12 months (Table 4.12).

FAS scores decreased between one and six months in 76.5% of participants who were fatigued at one month but not fatigued at six months and decreased in 86.7% of participants who were fatigued at one month but not fatigued at 12 months according to the case definition. However, FAS scores only decreased between six and 12 months after stroke onset in 40% of participants who were fatigued at six months but not fatigued at 12 months according to the case definition (Table 4.13).

These patterns suggest that, to some extent, changes in FAS scores mirror changes in fatigue status according to case definition.   In other words there is a relationship between a change in fatigue status as assessed by the case definition and change in FAS score.

Table 4.12 – Relationship between the change in fatigue status as assessed by case definition and change in FAS score.

Course of fatigue between one and six months according to case definition	**FAS score increased N (%)**	**No change in FAS score N (%)**	**FAS score decreased N (%)**	**Median (IQR) combined FAS score across the two time points.**
Fatigued at both time points (n = 10)	6 (60) Median increase = 9	-	4 (40) Median decrease = 6	60 (55-75)
Fatigued at one month but not fatigued at six months (n = 17)	4 (23.5) Median increase = 5	-	13 (76.5) Median decrease = 6	53 (47-56)
Not fatigued at one month but fatigued at six months (n=13)	7 (53.8) Median increase = 9	2 (15.4)	4 (30.8) Median decrease = 3	52 (39-64)
Not fatigued at either one month or six months (n = 61)	21 (34.4) Median increase = 3	5 (8.2)	35 (57.4) Median decrease = 5	40 (34.5-46.5)
Course of fatigue between one and 12 months according to case definition	**FAS score increased N (%)**	**No change in FAS score N (%)**	**FAS score decreased N (%)**	**Median (IQR) combined FAS score across the two time points.**
Fatigued at both time points (n = 10)	5 (50) Median increase = 7	1 (10)	4 (40) Median decrease = 4.5	62 (55-70)
Fatigued at one month but not fatigued at 12 months (n = 15)	1 (6.7) Median increase = 2	1 (6.7)	13 (86.7) Median decrease = 6	51 (40-62)
Not fatigued at one month but fatigued at 12 months (n=8)	6 (75) Median increase = 6	1 (12.5)	1 (12.5) Median decrease = 1	50 (41.5 – 60)
Not fatigued at either one month or six	26 (47.3) Median	3 (5.5)	26 (47.3) Median	42 (34-50)

months (n = 55)	increase = 3		decrease = 5	
Course of fatigue between six and 12 months according to case definition	**FAS score increased N (%)**	**No change in FAS score N (%)**	**FAS score decreased N (%)**	**Median (IQR) combined FAS score across the two time points.**
Fatigued at both time points (n = 10)	2 (20) Median increase = 3.5	1 (10)	7 (70) Median decrease = 7	60 (57-83)
Fatigued at six month but not fatigued at 12 months (n = 10)	6 (60) Median increase = 5.5	-	4 (40) Median decrease = 4	53 (47-69)
Not fatigued at six months but fatigued at 12 month (n=8)	8 (100) Median increase = 6.5	-	-	55 (46-62.5)
Not fatigued at either six month or 12 months (n = 61)	30 (50) Median increase = 3.5	8 (13.1)	23 (38.3) Median decrease = 3	38 (31-45)

Selective attrition

There was a significant association between presence of clinically significant fatigue at one month and non-attendance for the six month assessment (37% of those who fulfilled case definition versus 17% of those who did not fulfil case definition, p=0.015). There was no significant difference in one month FAS scores between those who attended and those who did not attend the 6 month follow-up (median 25, IQR 17-33 versus median 23, IQR 17.75-28.25, p=0.314). (Table 4.13)

Table 4.13 - Relationship between fatigue at one month and attendance at six months.

	Attended six months assessment	**Did not attend six month assessment**	**p-value**
Case definition at one month			
Yes	27 (63%)	16 (37%)	0.015[a]
No	74 (83%)	15 (17%)	
FAS scores at one month			
Median (IQR)	23 (18-28.5)	25 (17-33)	0.314[b]

a = Fisher's Exact Test

b = Mann-Whitney U

There was no relationship between fatigue (FAS or case definition) at one month and attendance at 12 months. There was also no association between fatigue (FAS or case definition) at six months and then attendance at 12 months (Table 4.14).

Table 4.14 - Relationship between one and six month fatigue and attendance at 12 months.

	Attended 12 month assessment	Did not attend 12 month assessment	p-value
Case definition at one month			
Yes	25 (58%)	18 (42%)	0.149[a]
No	63 (71%)	26 (29%)	
Case definition at six months			
Yes	20 (87%)	3 (13%)	0.740[a]
No	69 (84%)	13 (16%)	
FAS score at one month Median (IQR)	23 (18-29)	24 (17-29.75)	0.498[b]
FAS score at six months Median (IQR)	20 (17-25)	22 (18.25-27.5)	0.348[b]

a = Fisher's Exact Test

b = Mann-Whitney U

Discussion

This is the first study to investigate the frequency and natural history of clinically significant fatigue after stroke as assessed by a case definition.

Frequency of fatigue

The proportion of participants in the whole cohort with clinically significant fatigue decreased from 32.6% at one month to 19.8% at 12 months and the proportion of participants who attended all three assessments with clinically significant fatigue decreased from 27.9% at one month to 20.9% at 12 months. The systematic review of longitudinal studies of fatigue after stroke in Chapter 2 and a longitudinal study published subsequently reported the frequency of fatigue at the first time point to be much higher, ranging from 30.5% to 92% (Duncan et al. 2012; Radman et al. 2012).

All these other longitudinal studies used a single question or a cut-off point on a scale to determine if a participant was fatigued rather than use a case definition which has much more discriminating criteria and this may explain why a lower frequency of fatigue was found in this study. The case definition's criteria may have been too strict and as a result failed to identify some participants with problematic fatigue. For instance, a person may feel fatigued for less than 50% of the day or feel fatigued only two days a week and yet still feel that fatigue is a major problem for them. Indeed, the fact that 62%, 49% and 54% of participants in this study scored 22 or above (the commonly used cut-off score (De Vries et al. 2004)) on the FAS at one, six and 12 months respectively and the fact that this is much higher than the percentage of participants who fulfilled the case definition, does suggest that using the case definition has led to an underestimation of the frequency of clinically significant fatigue. It may be worth considering making slight changes to the case definition to make the criteria less strict such as excluding certain questions or by lowering the threshold of fulfillment to feeling fatigued only for 40% of the day or only two days a week. However any changes made to the case definition would have to be carefully considered as if the threshold for fulfillment was lowered by too much then this could result in people without a particularly problematic fatigue meeting all the case definition criteria and the frequency of clinically significant fatigue being overestimated (Brurberg et al. 2014).

It is also possible that using the case definition resulted in a lower frequency of fatigue than the frequency reported in studies which used cut-offs on multi-item scales because the case definition approach is simply better at detecting fatigue than the cut-off method and consequently the frequency of fatigue in this study more accurately reflects the extent of fatigue after stroke than studies that used a cut-off. It has been previously mentioned that using cut-offs can be problematic as important information can be lost. In this study some people who scored above the cut-off on the FAS said in their fatigue case definition interview that fatigue wasn't a problem for them. This illustrates how important information can be lost by using cut-offs and that using a case definition approach may provide more detailed and therefore more accurate information.

In the cancer related fatigue literature estimates of the prevalence of fatigue obtained by using a case definition are also generally much lower than estimates obtained by other methods such as a multi-item scale (Andrykowski et al. 2005).

Natural History of Fatigue

The findings of this study suggest that the frequency of clinically significant fatigue decreases over the first year after stroke. This decrease in frequency of fatigue is consistent with the results of most of the longitudinal studies identified in the review in Chapter 2. Seven of the nine studies (n=764) reported a decrease in the number of people who were fatigued over time whereas only two of the studies in the review (n = 195) and the longitudinal study published since the review was completed (n=109) reported the frequency of fatigue to increase over time (Duncan et al. 2012; Radman et al. 2012).

However even though the frequency of fatigue decreases over time, in this study it was still present in approximately a fifth of stroke patients at the 12 month time point and this finding that fatigue can persist in the long term is consistent with all other longitudinal studies of fatigue after stroke.

Interestingly, by breaking down the case definition into its individual questions it could be seen that although a similar proportion of participants at each time point reported experiencing fatigue every day or nearly every day, as time went on more participants reported that their fatigue was present for less than 50% of the day. This illustrates further the experience of fatigue for a stroke survivor over the course of the first year.

Individual Course of Fatigue

Investigating the natural history of fatigue for individuals revealed that most participants (60.4%) were either fatigued or not fatigued across all three time points meaning that fatigue status fluctuates in 39.6% of participants across time points. This is consistent with three other longitudinal studies which reported that most (55%, 83%, 75%) of patients were either fatigued or not fatigued across all time points (Schepers et al. 2006; Snaphaan, van der Werf and de Leeuw 2011; Christensen et al. 2008).

A pertinent finding of examining the course of fatigue for individuals is that most (16 out of 24) of the participants who had clinically significant fatigue at one month did not have it at the six month assessment indicating that most stroke survivors will recover from fatigue that they consider to be problematic and that clinically significant fatigue is not inevitable in the long term. Conversely, this study also found that only one in five participants who were not fatigued at one month went on to develop clinically significant fatigue at either the six or 12 month assessment indicating that stroke survivors who do not have clinically significant fatigue at one month are not likely to develop it within the first 12 months and that it is still possible to develop clinically significant fatigue after the one month time point.

These findings suggest that the likely mechanisms of fatigue after stroke may be more complex than the de-conditioning model which was proposed in Chapter 1. Potential mechanisms will be discussed in more detail in Chapter 6.

Fatigue severity (FAS scores) and relationship between FAS scores and case definition fulfilment.

Fatigue severity as assessed by the FAS significantly decreased between the one and six month time points, although FAS scores did increase in some individuals.

As might be expected, this study found there to be a relationship between case definition fatigue status and fatigue severity. At all three time points, participants with clinically significant fatigue had significantly higher FAS scores than those who did not report clinically significant fatigue.

Moreover, there is a relationship between change in fatigue severity (FAS scores) and change in fatigue status when the course of fatigue across time points for each individual is examined. If a participant changed fatigue status from fatigued to not fatigued across two time points, in most cases their FAS score was likely to decrease across the two time points and increase if their fatigue status changed from not fatigued to fatigued. This is important as it suggests that case definition fulfilment is related to fatigue severity as opposed to being related to a participant's ability to adapt their lifestyle to fatigue so that fatigue is no longer a problem for them.

The results indicate that a change in fatigue status as assessed by the case definition is associated with a change in FAS score in most individual participants.

Strengths of Study

This study has several strengths. It is a prospective, longitudinal study, participants were recruited very soon after stroke onset. Another strength of this study is that two instruments were used for assessing fatigue; the fatigue case definition and the fatigue assessment scale. Both of these instruments have been validated and tested for reliability and feasibility in stroke patients (Mead et al. 2007; Lynch et al. 2007).

Limitations of study

One limitation of the study was the smaller than anticipated number of people that were recruited to the study. If more people had been recruited a more precise measure of fatigue frequency would have been obtained.

It is also a limitation of this study that participants who had clinically significant fatigue at one month were more likely to drop-out of the study by six months. This means that it is likely that this study has underestimated the frequency of clinically significant fatigue at the six and 12 month time points. However FAS scores did not predict whether a participant would drop-out of the study. Also the frequency of fatigue at each time point for just the 86 participants who attended all three assessments was similar to the frequency of fatigue for the whole cohort.

Interestingly participants who said that they had a problem with fatigue before their stroke were significantly more likely to attend all three assessments than those who said they did not have a problem with fatigue before their stroke. It is plausible that people who had long term fatigue problems may have had more interest in taking part in a fatigue study than participants that had not had previous fatigue problems. However, this indicates a limitation of the study as a drop out bias towards participants who did not have fatigue problems before their stroke could mean the frequency of fatigue has been over-estimated at the six and 12 month time points.

A potential limitation of this study is that although most participants were recruited to the study within a week of stroke onset (Median 5 days, IQR 3-8 days), some (n=24) participants were recruited between 14 and 30 days after their stroke. The participants who were recruited later were mostly recruited from one of the rehabilitation hospitals. The main reason they were being recruited at these hospitals at a later time point was that they were too ill in the first week after their stroke for them to be approached on the acute ward. This method of recruitment introduces a potential bias in the study as these participants may have had different characteristics from participants who were recruited in the first few days after their stroke and discharged home or patients who were not recruited in first few days perhaps due to dysphasia but still discharged home. It is plausible that some of these characteristics could have an influence on a participant's fatigue levels i.e. higher disability levels. In addition, at recruitment the participants answered questions regarding pre-stroke fatigue and pre-stroke activity levels. Those who were recruited at a later time point may have been more susceptible to recall bias when answering these questions than participants who were recruited at an early time point after stroke.

Another potential limitation of the study is that the same researcher carried out all follow-up assessments which means that "carry-over effects" could have created biases in the data which was collected. For instance, the researcher may have remembered what each participant said about fatigue at a previous assessment and this could have unintentionally influenced how the participants described their fatigue at their current assessment. However this is unlikely to have taken place as the researcher carried out many fatigue interviews which meant that it wasn't possible to remember what each participant had said and when the participants were asked to fill out questionnaires during an assessment, the researcher did not look at the participants' questionnaire answers (the researcher did enter the data into the SPSS database but this was at a later point and there was only participant ID numbers and not names on the questionnaires when this was taking place).

A final limitation of the study is that the findings cannot be generalised to stroke survivors who have had more severe strokes as the sample in this study consisted mainly of those who had experienced strokes that could be described as mild to moderate in severity. This is because many patients with severe strokes would not have met the inclusion criteria (too aphasic, lack of mental capacity). Patients with more severe strokes and who still met the inclusion criteria were approached and asked to take part in the study. However anecdotal feedback from some people in this subgroup of patients indicated that they were discouraged from taking part due to their impairments for example they were unable to read information sheet for themselves.

Conclusions

In summary, clinically significant fatigue is a common symptom in stroke survivors which may resolve in most individuals but persist in a minority over the first year after stroke.

Potential reasons why fatigue may either persist or resolve will be discussed further in Chapter 5 and Chapter 6.

Summary of Chapter 4

Background and aims

- Previous longitudinal studies have not investigated the natural history of clinically significant fatigue after stroke.
- This chapter aimed to determine the frequency, severity and natural history of clinically significant fatigue in the first 12 months after stroke onset.

Method

- Patients with a recent acute stroke were recruited from hospitals in Edinburgh, Scotland.
- At one, six and 12 months after stroke onset a structured interview was performed to identify clinically significant fatigue (case definition) and the Fatigue Assessment Scale (FAS) was administered to assess fatigue severity.

Results

- At one month 33% had clinically significant fatigue.
- Eighty-six participants attended all three assessments, of whom clinically significant fatigue was present in 28% at one month, 23% at six months and 21% at 12 months. Their median (IQR) scores were 23 (18-29), 21 (17-25) and 22.5 (17-28) at one, six and 12 month respectively.
- Of 101 participants who attended at least the one and six month assessments, fatigue status did not change in 64%, fatigue status changed from fatigued to non-fatigued in 15% and changed from non-fatigued to fatigued in 9%.

Conclusions

- Clinically significant fatigue affected a third of patients one month after stroke. About two thirds of these patients had become non-fatigued by six months, most of whom remained non-fatigued at 12 months.
- Clinically significant fatigue was present in a fifth of the whole cohort at 12 months.

Chapter 5 – Exploratory longitudinal cohort study of associations of fatigue after stroke.

Data from this chapter have been published in Stroke. The full paper (Duncan et al. 2015) has been included as an appendix (Appendix 15).

Contributions to the study

The study was designed by Professor Gillian Mead with help from Professor Martin Dennis, Professor Alasdair MacLullich, Dr Susan Lewis, Dr Carolyn Greig and Professor Michael Sharpe.

The PhD candidate:

- recruited all participants except for three who were very kindly recruited by Dr Mansur Kutbaev.
- collected all data at time of recruitment by administering questionnaires, the MMSE and NIHSS as well as directly from patients' medical notes
- obtained informed consent
- arranged and carried out all follow-up assessments i.e. collected all data.
- entered all data into SPSS database
- carried out the some of the statistical analysis in this Chapter however most of the statistics in this Chapter were done by Professor Gordon Murray and Dr Susan Lewis.

This work was supported by the Chief Scientist Office of the Scottish Government.

Abstract

Background and Purpose: The aetiology of post-stroke fatigue is unclear. In this prospective study it was explored whether reduced physical activity and/or physical fitness might contribute to post stroke fatigue, or be a consequence of it.

Methods: Patients with a recent acute stroke were assessed at one month, 6 months and 12 months with the Fatigue Assessment Scale (FAS), a fatigue case definition, the Hospital Anxiety and Depression Score, the Epworth sleepiness scale, the EuroQoL quality of life measure, hand grip dynanometer, a measure of leg strength, a measure of leg power, the 6MWT and accelerometry (ActivPAL^{TM}). Bivariate analyses determined associations between fatigue and step count and between fatigue and fitness at each time point. Multiple linear regression tested whether one month step count independently predicted 6 and 12 months FAS.

Results: 136 participants (mean age 72 years, 64% men) attended at least one assessment. ActivPAL data were available for 84 (64%), 69 (66%) and 58 (64%) participants at one month, six months and 12 months respectively. At six and 12 months, a positive fatigue case definition was associated with lower daily step counts (p=0.014 and 0.013 respectively). At one, six and 12 months, higher FAS (more fatigue) was associated with lower step count (p<0.001, 0.01 and 0.007), higher depression (p<0.001), anxiety scores (p<0.001) and sleepiness (P<0.001) and poorer quality of life (p<0.001). Lower daily step count (p<0.002 and 0.006) and greater anxiety (p<0.001 for both) at one month independently predicted higher FAS at six and 12 months. No significant associations were found between fatigue and any of the measures of fitness.

Conclusions: Lower step counts at one month and higher levels of anxiety at one month independently predicted greater FAS for up to 12 months. Physical activity and anxiety levels might be therapeutic targets for post-stroke fatigue.

Rationale

The systematic review in Chapter 3 of this thesis identified that only eight studies have investigated the relationship between post-stroke fatigue and activity and/or fitness (Miller et al. 2013; Hoang et al. 2012; Robinson et al. 2011; Lewis et al. 2011; Tseng et al. 2010; Michael and Macko 2007; Michael, Allen and Macko 2006; Shaughnessy, Resnick and Macko 2006).

These studies had several limitations. For instance, none of them were longitudinal in design meaning that associations between fatigue and activity and/or fitness over time could not be identified, some had very small samples sizes (Hoang et al. 2012; Tseng et al. 2010), only one included a measure of muscle power (Lewis et al. 2011) and none included a measure of muscle strength which means that fatigue related to any de-conditioning which might have occurred would not have been detected in all but one of the studies. None of these studies measured how much activity participants were doing before their stroke or whether they were fatigued before their stroke which are potentially important confounders of the relationship between post-stroke fatigue and post-stroke activity and/or fitness. In addition, only three of these studies controlled for depression (Lewis et al. 2011; Robinson et al. 2011; Tseng et al. 2010), none of them specifically controlled for anxiety and only two controlled for age and gender (Robinson et al. 2011; Lewis et al. 2011).

Therefore the review showed that this area of research is an emerging field but that there is still not sufficient evidence to conclude that post-stroke fatigue is associated with low levels of activity and/or fitness or conclude which factors may influence such a relationship. As previously mentioned in Chapter 3, it is important to establish whether or not such an association exists as this may establish whether an activity-based or fitness-based intervention for fatigue is promising.

Study aims

The aims of this part of the longitudinal study were to investigate:

a) the physical activity levels of stroke patients at three time points over the first year and determine whether they are associated with chronic fatigue.

b) the physical fitness levels (specifically leg strength, leg power, hand grip strength, aerobic fitness) of stroke patients at three time points over the first year and determine whether they are associated with chronic fatigue.

c) the relationship between patient characteristics measured at baseline, time of recruitment or the one month follow-up and fatigue at later time points.

(As in Chapter 3 of this thesis, this longitudinal study was interested in relationships between chronic fatigue and physical activity and/or physical fitness as opposed to muscle or exertion fatigue).

Method

Design

The design of this study is described in Chapter 4.

Participants

The method of recruiting participants and the inclusion/exclusion criteria are described in Chapter 4.

Measurements

The following measurements were taken directly from the participants at the time of recruitment or at the follow-up assessments in addition to the ones already described in Chapter 4.

Ethical Approval

Approval from Lothian Research Ethics Committee was obtained (Appendix 22) and all participants gave written informed consent.

Measurements taken at time of recruitment

At the time of recruitment to the study, the Physical Activity Scale for the Elderly (PASE) was used to measure pre-stroke physical activity. The PASE (Washburn et al. 1993) is a self-report instrument where participants indicate how many of the seven days prior to stroke onset and how many hours a day on average they spent in sitting activities, walking outside their home, doing light, moderate or strenuous recreational or sporting activities or doing exercises specifically to increase muscle strength or endurance. The PASE also asks participants if they carried out any light or strenuous household chores, household repairs, gardening, cared for a dependent individual or did any work for pay or as a volunteer in the seven days before they had their stroke. A total score for each participant is calculated by using a scoring algorithm which was specifically derived for the PASE. The scores range from 0 to 360 (Siordia 2012). This score represents an overall estimate of an older person's physical activity level and a higher score indicates greater physical activity. The PASE was chosen as it had been previously used with stroke patients (Boysen et al. 2009; Krarup et al. 2007) and, although it has not been extensively validated in stroke patients, one study reported that the PASE moderately correlates with the items in the Senior Fitness Test that require strength, endurance and balance and therefore validly reflects overall physical capacity to perform everyday activities that require these characteristics (Lindahl et al. 2008).

Measurements taken during follow-up assessments

Physical fitness

Muscle strength measurement

The specific aspect of muscle strength that was being assessed was the participant’s maximum voluntary isometric knee extensor strength (Skelton et al. 1995).

This was measured by asking participant’s to sit in a chair which was raised above the floor and to position their knee at an angle of 90 degrees. A linen cuff was hooked around their ankle and this was attached to a strain gauge by a chain. This strain gauge was attached to Chart 4.0 software via a data acquisition system (Powerlab, AD instruments). Velcro straps were placed over the pelvis of participants to hold it in the correct position during measurements. The participant was then instructed to push their leg against the cuff as hard as they could for five seconds and a measure (in Newtons) of maximum voluntary knee extensor strength was taken. Although this study was interested in the leg that was not affected by the stroke, three measurements were taken on each leg. The highest score for each leg was recorded as the maximum voluntary strength.

Muscle power measurement

The amount of explosive power that participants had in each leg was measured using the Nottingham Leg Extensor Power Rig (Bassey and Short 1990). This instrument was used as it was specifically designed so that it can be safely used by older people.

Before the power measurement was taken, the weight of the participant (in kilograms) was measured using digital scales. The participant was then asked to sit on the power rig and the distance between the chair and the footplates was adjusted so that when the participant's pushed the footplate as far as it could go, their leg was nearly completely extended. Participants were then instructed to place one leg on one of the footplates and on the researcher's signal to push the footplate down as hard and as fast as they possibly could. This action would start-up a flywheel which was attached to an analog-to-digital converter and using specialist software the amount of explosive effort of each leg measured in Watts per kg of body weight was obtained. Five measurements were taken on the right leg and then five were taken on the left leg. The highest value for each leg was recorded.

The Nottingham Power rig has been found to be a feasible method of measuring lower limb extensor power in stroke patients (Lewis et al. 2011; Saunders et al. 2008). The repeatability of this method has also been previously established in stroke patients (Greig et al. 2003).

Aerobic Fitness

Participant's aerobic fitness was measured by using the Six Minute Walk Test (6MWT) (Hutcheon et al. 2002). Participants were taken to a hospital corridor which had been measured and a marker placed at every metre. They were instructed to walk at "as fast a pace as they can manage" along the length of the corridor for a time period of six minutes. The distance in metres walked in the time is recorded. Participants were informed that they can stop or rest if they need to but the clock will keep running. The researcher only spoke to participants during the walk at one minute intervals to tell them how many minutes they had left to go. On the assumption that participants do actually walk as fast as they can, the 6MWT is a good measure of aerobic exercise capacity.

Several studies have reported the 6MWT to have excellent test-retest reliability in stroke patients (Wevers et al. 2011; Fulk et al 2008; Flansbjer et al. 2005; Eng et al. 2004). It has also been reported to have excellent concurrent validity with 10 meter comfortable gait speed, 10 meter fast gait speed, stair climbing ascend, stair climbing descend (Flansbjer et al. 2005) and maximum oxygen consumption (Eng et al. 2004).

Hand grip strength

Hand grip strength was measured by using a Baseline 200lb standard head hydraulic hand dynamometer with the handle set to position 3 for all participants. The researcher first demonstrated how to use the dynamometer. Participants then held the dynamometer in a sitting position with their elbow at a 90 degree angle. They were then instructed to squeeze the hand grip dynamometer as hard as possible for 3 seconds. Three measurements were taken alternating between the left and the right hand. The highest score (kilograms) for each hand was recorded as their maximum hand grip strength.

The Baseline hydraulic dynamometer has been reported to have acceptable inter-instrument reliability and concurrent validity with the Jamar hydraulic dynamometer (Mathiowetz, Vizenor and Melander 2000) which has established test-retest, inter-rater and intra-rater reliability (Roberts et al. 2011).

This study was interested in the fitness measurements of the side of the body which was not affected by stroke. Participant's non-affected side was identified by examining the following sources of evidence:

1) patient medical records on admission were examined to see what side the patient or the attending doctor had reported as being affected on admission.
2) At the one month assessment each participant was asked which side they felt had been affected by the stroke.

After following this procedure we were still unable to identify an affected side for 25 participants. For these participants the mean score of their left and right sides was used in each analysis.

Physical Activity

Free living physical activity was measured by asking participants to attach a lightweight accelerometer (ActivPAL™, PAL Technologies Ltd; Figure 5.1) to the thigh of their unaffected leg. The ActivPAL™ was chosen as it can be directly stuck onto a participant's skin instead of being attached to an item of their clothing, and therefore is less of a burden to the participant, who may have functional limitations, than an accelerometer that needs to be attached and unattached every day.

Participants were asked to wear the ActivPal™ for 7 days before returning it to the researcher in a pre-paid envelope if they were at home or the researcher would collect it from them if they were still in hospital. The ActivPAL™ records the amount of time a participant spends sitting or lying, standing upright, stepping and number of steps taken per day over the seven day period. The first and last calendar days of recorded data were excluded as these represented incomplete 24 hour periods and data from the middle calendar days were used in the analysis. All participants were asked to wear the ActivPAL™ even if they were unable to walk.

The ActivPAL™ has been reported to be a valid, reliable and feasible tool for measuring ambulation in community-dwelling stroke survivors (Mahendran et al. 2016).

Figure 5.1 - ActivPAL™ accelerometer. (Photo courtesy of Pal Technologies Ltd)

Additional Questionnaires

Participants were also asked to complete the following questionnaires during their assessments.

Hospital Anxiety and Depression Scale (HADS).

The HADS (Zigmond & Snaith 1983) is a self report questionnaire consisting of seven questions for anxiety and seven for depression. For each item the participant's response is scored from 0-3. These scores are summed to give a total anxiety and a total depression score. For each scale scores of 0-7 are considered normal, 8-10 are considered borderline and scores of 11 or above indicate a problem with anxiety and/or depression.

One advantage of using the HADS in this study as opposed to other measures of mood such as the Geriatric Depression Scale or the Beck Depression Inventory is that, unlike these instruments, the HADS does not have an item which relates to fatigue or loss of energy.

The HADS has been reported to be an acceptable screening instrument for depression in stroke patients (Aben et al. 2002) and one systematic review of mood screening tools for stroke survivors reported that the HADS was the only effective tool to identify anxiety (Burton and Tyson 2015).

The Epworth Sleepiness Scale

The Epworth Sleepiness scale (Johns 1991) is used to determine the level of daytime sleepiness. It consists of eight everyday situations and the participant is required to say whether there is no chance (score 0), a slight chance (score 1), a moderate chance (score 2) or a high chance (score 3) of them dozing off in each situation. A total score of six or below suggests the respondent is getting enough sleep whereas a score of ten or more is suggestive of a sleep disorder.

The Epworth Sleepiness Scale was chosen as it had been previously used with stroke patients (Hsu et al. 2006). The scale has been reported to be reliable and have good construct validity for use in stroke patients and therefore can be used to detect cases of pathological sleepiness in stroke (Mills et al. 2013).

Quality of Life (EuroQoL)

The EuroQol 5D-3L (Group TE, 1990) is a generic health related quality of life instrument. Participants respond to questions on mobility, self care, usual activities, pain and anxiety and depression by indicating which of three hierarchical statements is most appropriate to their circumstances. The final question asks participants to indicate which number between 0 and 100 best describes their overall health (100 being best health possible). The EuroQoL has been reported to have acceptable concurrent and discriminant validity and acceptable test-retest reliability for the measurement of health-related quality of life after stroke (Dorman et al. 1998; Dorman et al. 1997).

These instruments and questionnaires were presented to participants in the same order each time i.e. the fatigue case definition interview, the FAS questionnaire, the Epworth sleepiness scale, the EuroQoL and then the HADS. The HADS was presented last as it was felt that the questions on anxiety and depression may possibly influence participant's perceptions of their fatigue.

Practical Constraints

It was not possible to perform the tests of leg extensor strength and leg extensor power on participants who were followed-up in their own home or in a rehabilitation hospital as the necessary equipment for these tests were not portable.

It was also not possible to perform the Six Minute Walk Test during follow-up assessments which took place in participant's own homes due to safety concerns.

Preparing data for analysis

Data Checking

The procedures for data checking are described in Chapter 4.

Procedure for dealing with missing values in the database

The procedure for dealing with missing values in the dataset when a participant did attend an assessment but missed out either answering a question or doing a test are described in Chapter 4.

Normality Checks

The procedures for checking the normality of the data are described in Chapter 4.

Transformations

The normality checks revealed that the FAS scores at each time point were positively skewed and therefore a transformation (log base 10) was performed to produce normally distributed data (Table 5.1).

Table 5.1 – Details of transformations performed on variables.

	Distribution before transformation	**Transformation performed**	**Result of transformation**
Fatigue Assessment Scale (FAS) scores at each of the three time points.	Positively skewed	Log-10 transformation	Data now normally distributed.

When the distributions of the other measures were examined it was found that some of the distributions were normal and some were positively skewed. A fundamental assumption of parametric statistical tests is that data are normally distributed.

Therefore transformations to turn the skewed distributions into normal distributions were attempted. However for some measures a log transformation did not work and a square root transformation was required and other measures could not be successfully transformed into a normal distribution at all. The details of the distributions of each measure and which transformations were attempted are presented in Appendix 16.

Therefore to avoid any problems which could arise from using a mixture of transformation methods across the independent variables in the analyses and on the advice of Professor Gordon Murray (Professor of Medical Statistics, University of Edinburgh), transformed FAS scores were used but the data for any of the independent variables were not transformed. Consequently, non-parametric statistical tests were used to investigate many of the relationships and comparisons in this study.

The main implication of using non-parametric tests instead of parametric tests is that there is a higher likelihood of making a Type II error (failing to find a relationship which does exist) which means parametric tests were used whenever possible.

Statistical Analysis

The statistical analysis was overseen by Dr Susan Lewis (Statistician, Department of Geriatric Medicine, University of Edinburgh) and Professor Gordon Murray (Professor of Medical Statistics, University of Edinburgh).

Activity Data

The mean amount of time spent stepping, standing and sitting or lying each day and the mean number of steps taken each day for each participant were calculated.

Changes in fitness and activity over time

The medians and IQR of participants' scores on each of the activity and fitness measures at each time point were calculated and tabulated to determine whether these scores changed over time. The differences in fitness and activity scores across time points were investigated by using the Friedman's test.

Uni-variate relationship between baseline measures and fatigue

The relationships between each baseline variable which was measured with continuous data and log-transformed FAS scores at one, six and 12 months after stroke onset were investigated using Spearman's rho correlations. The differences in log-transformed FAS scores between different baseline categories were investigated by using independent samples t-tests.

Associations between the baseline variables and the presence of fatigue as assessed by the fatigue case definition at the one, six and 12 month time points were investigated using either independent samples t-tests, a Mann-Whitney U or chi-square (Fisher's exact) tests.

The stroke subtype variable was coded into two categories: those participants who were diagnosed with a POCS and those participants who were diagnosed with one of the other three subtypes (LACS, TACS and PACS). This was done as previous studies had indicated a possible association between posterior strokes and fatigue after stroke (Kutlubaev, Duncan and Mead 2012).

Uni-variate relationships between characteristics measured at the follow-up assessments and fatigue

The relationships between the characteristics measured at one, six and 12 months and log-transformed FAS scores at each equivalent time point were investigated using two-tailed Spearman's correlations.

The differences between those who did and those who did not fulfil the fatigue case definition on each measure taken were investigated using Mann-Whitney U tests.

Due to the large number of statistical comparisons being made in this analysis, the level of statistical significance was set at $p < 0.01$ instead of $p < 0.05$ in order to decrease the likelihood of a Type I error being made (finding a statistically significant result, when in fact, no genuine difference or relationship exists in the population (Field 2005)). It could be argued that the significance level when many comparisons are being made should be ascertained by using a Bonferroni correction (where each test conducted uses a particular alpha level (normally 0.05) divided by the number of tests conducted to control the overall Type I error rate). However, the number of comparisons in this analysis would mean the calculated Bonferroni correction signficance level would be so small that using this level would have increased the likelihood of a Type II error (not finding a genuine difference or relationship in the population when, in fact, one does exist) being made to an unacceptable level. Therefore instead of carrying out a Bonferroni correction an arbitrary decision was made to use the $p < 0.01$ significance level.

Multi-variate analysis

A multiple regression analysis was performed to determine which measures taken at baseline, recruitment or at the one month time point could predict log-transformed FAS scores at the six and 12 month time points.

As previously reported in Chapter 4, some participants were lost to follow-up and the six and 12 month time points were only attended by 105 and 91 participants respectively and this creates the problem of the dependent variable of the multiple regression models having a lower number of cases and therefore lower power and this smaller subset of the data may potentially have a healthy survivor bias. Therefore to address these issues and on the advice of Professor Gordon Murray (Professor of Medical Statistics, University of Edinburgh) the Expectation Maximisation (EM) single imputation method (Dempster, Laird and Rubin 1977) was used to replace log-transformed FAS total scores that were missing due participants not attending an assessment. EM imputation is a two step iterative process. The first step estimates the parameters of the distribution of the missing data by using the actual values of the observed data. The second step imputes an expected value and then determines whether this value is the most likely value and if it is not then the procedure is repeated until the most likely value has been found (Lin 2010). EM is a technique which is regularly used to manage missing data (Psychlopedia). It is considered to be more effective than other methods of imputation such as mean imputation or Last Observation Carried Forward as it is less likely to produce biased estimates such as underestimation of the standard error (Gold and Bentler 2000) and it maintains the relationships with other variables which is very important when carrying out a regression analysis (The Analysis Factor).

The procedure for the EM analysis was carried out in the Missing Value Analysis option in SPSS. The log-transformed FAS total scores for all three time points were selected. Little's MCAR test for EM statistics was performed before the missing values were imputed.

Procedure for selecting potential independent variables for multiple regression models

Once the missing values had been imputed into the log-transformed FAS scores, Spearman's correlations or t-tests were used to determine which of the measures taken at baseline, recruitment or at the one month assessment were significantly associated with log-transformed FAS scores at the six and 12 month time points. The measures found to be significant ($p < 0.01$) were selected as potential independent variables for the multiple regression models.

Additional variables which were not significantly associated with fatigue but were considered to be of fundamental importance were also included in the regression models.

Assumptions of regression

In the regression analyses in this chapter, the following assumptions were checked: The assumption of multicollinearity was checked by examining the VIF (Variance inflation factor) and tolerance statistics in the SPSS output. Additionally the assumption of multicollinearity was checked by examining Spearman's correlations between all potential independent variables to ensure that they did not correlate with each other too highly (i.e. 0.8 or above). Multicollinearity refers to a situation where two or more independent variables are too highly correlated with each other. This can be problematic when these variables are predictors in a regression model. For instance, multicollinearity can increase the likelihood that a predictor variable which is related to the outcome will be found non-significant and rejected from the model i.e. a Type II error is more likely to occur. Multicollinearity can also result in it being impossible to determine which of two highly correlated predictors is more important as each one would have a similar effect on the regression model (Field 2005).

The assumption of independent errors was checked by using the Durbin-Watson test.

The assumption of normally distributed errors was checked by examining histograms and Normal P-P Plots that the SPSS output produced.

The assumptions of linearity and homoscedasticity were checked by examining the scatterplots of standardised residuals against standardised predicted values that the SPSS output produced.

An additional assumption that must be met before performing statistical tests is that data from different participants are independent. As all participants attended assessments separately and no participant was given details of any other participant it is highly unlikely that any of them could have had the opportunity to discuss the study and influence each other. Therefore we can be confident that this assumption has been met.

Method of regression

On the advice of Professor Gordon Murray and Dr Susan Lewis a hierarchical approach was used for entry of the predictors into the multiple regression models. This involved putting the variables age, gender and fatigue before stroke into the model using the Enter method and at the next step entering all the other variables into the model and using the Stepwise method to explore which independent variables were contributing most to the model. In the final regression models, all independent variables were entered during the same step.

Results

The number of participants that were recruited and that were lost to follow-up were the same as described in the results section of Chapter 4.

The timing, location and duration of follow-up assessments are also described in the results section of Chapter 4.

As described in Chapter 4, the Clinical Research Facility (CRF) was attended by 69 (52.3%), 55 (52.4%) and 46 (50.5%) participants at the one, six and 12 month follow-ups respectively. Thirty two (24.2%) of participants completed the one month assessment in a rehabilitation hospital. The rest of the participants were seen in their own homes. This had implications for collecting data on aspects of physical fitness as it was not possible to perform tests of leg muscle strength, leg muscle power and distance walked in six minutes unless a participant attended the CRF for their follow-up assessments. This was because the equipment for measuring leg strength and power were too large to be taken out of the CRF and the six minute walk test had to be performed in the hospital as it was a safety requirement of this test that a trained nurse was present as well as the researcher. Consequently, leg strength data was obtained for 66 (50%) participants at one month, 53 (50.5%) participants at six months and 43(47.3%) participants at 12 months, leg power data was obtained for 65 (49.2%) participants at one month, 53 (50.5%) participants at six months and 45 (49.5%) participants at 12 months and six minute walk data was obtained for 58 (43.9%) participants at one month, 46 (43.8%) participants at six months and 34 (37.4%) participants at 12 months.

An attempt was made to collect activity data from all participants. However, activity data were only collected for 84 (63.6%), 69 (65.7%) and 57 (62.6%) participants at the one, six and 12 month follow-up assessments respectively. There were at least five days of valid ActivPAL™ data for 65 participants at one month, 48 participants at six months and 44 participants at 12 months. In the remaining participants there was at least one whole day of activity data available.

Participants who attended at least one assessment but did not provide activity data at the one month time point had significantly higher baseline NIHSS scores than participants who did provide activity data ($p = 0.002$). None of the other baseline characteristics were associated with not providing activity data (Table 5.2).

Table 5.2 – Characteristics of participants who provided activity data at one month compared with participants who attended at least one assessment but did not provide activity data at one month.

Participant characteristic	Participants who attended at least one assessment but did not provide activity data (n = 52)	Participants who did provide activity data and are therefore included in regression analyses (N=84)	p-value
Median age, years (IQR)	66.0 (61.2-74.9)	72.3 (65.2-80.5)	0.217
Male (%)	20 (38.5)	56 (66.7)	0.583
First ever stroke (%)	39 (75.0)	67 (79.8)	0.530
Inpatient (%)	49 (94.2)	75 (89.3)	0.372
Ischaemic stroke (%)	46 (88.5)	81 (96.4)	0.085
Right hemisphere (%)	26 (50.0)	41 (55.4), n = 74	0.854
TACS (%)	1 (1.9)	4 (4.8)	
PACS (%)	28 (53.8)	29 (34.5)	
LACS (%)	14 (26.9)	26 (31.0)	0.125
POCS (%)	9 (17.3)	25 (29.8)	
Fatigue before stroke (%)	21 (40.4)	36 (42.9)	0.859
Diabetes history (%)	8 (15.4)	15 (17.9)	0.816
Hypertension history (%)	30 (57.7)	41 (48.8)	0.378
Median MMSE (IQR)	27 (25-28), n = 49	27 (25-29), n = 72	0.933
Median NIHSS (IQR)	3 (2-5), n = 52	2 (1-3), n = 82	**0.002**
Median PASE (IQR)	95 (41-157.8), n = 52	96 (59-158), n = 83	0.978
Mean systolic BP at admission (SD)	145.4 (22.9), n = 50	149.0 (28.6), n =79	0.460
Mean Diastolic BP at			

admission (SD)	82.6 (15.3), n = 50	78.2 (14.4), n = 79	0.103
Median Social deprivation rank (IQR)	3627.5 (1652.8-5364.8)	4789.50 (2447.75 – 6200.75)	0.217

TACS = total anterior circulation syndrome, PACS = partial anterior circulation syndrome, LACS = Lacunar syndrome, POCS = posterior circulation syndrome

MMSE = Mini Mental State Examination

NIHSS = National Institute of Health Stroke Scale

PASE = Physical Activity Scale for the Elderly

BP = Blood Pressure

Bold type = p < 0.01.

Activity and Fitness Data

The patterns for each of the activity or fitness measures across time points were similar. Participants' median scores for each activity or fitness measure were at their lowest at the one month time point and at their highest at the 12 month time point. Indicating that collectively, participants increased their activity levels and their physical fitness improved as time went on (Tables 5.3-5.6, Figures 5.2-5.6). However a Friedman's test revealed that the six minute walk test was the only activity or fitness measure where there was a significant difference in scores across the time points. Wilcoxon post hoc tests revealed participants walked a significantly further distance in six minutes at the six month time point than at the one month time point ($p<0.0001$) and significantly further at the 12 month time point than at the one month time point ($p<0.0001$) (Table 5.7).

Table 5.3 - Number of steps taken per day at each time point

		One Month	Six Months	12 Months	p*
Steps taken per day	Median IQR N	2841.4 1418.9-5722.9 84	4047.2 2055.9-5822.0 69	4362.00 2142.7-7011.2 57	0.922
Male	Median IQR N	2985.2 1418.9-5739.9 56	3927.5 1802.9-7503.2 42	4266.3 2637.3-7954.0 35	1.000
Female	Median IQR N	2814.2 1293.2-4853.7 28	4047.2 2104.7-5633.3 27	4536.5 1550.8 - 6193.0 22	0.829

*Friedman's test

Figure 5.2 – Median number of steps taken per day

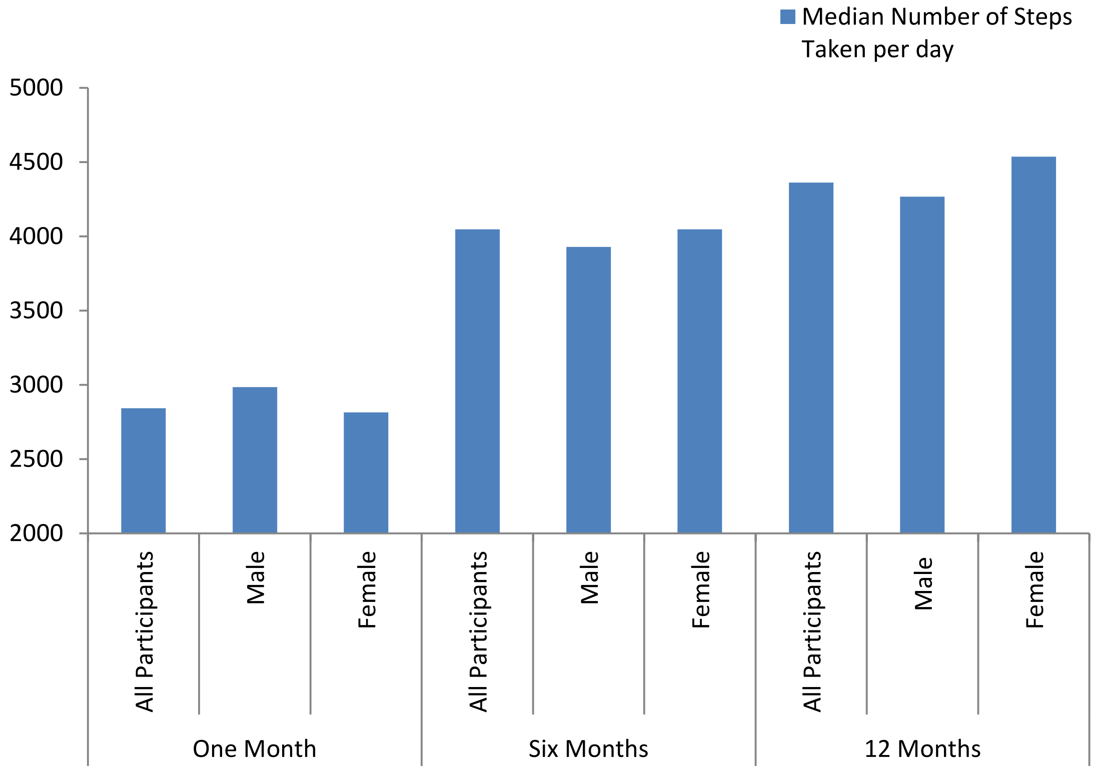


Table 5.4 - Hand grip strength scores at each time point

		One Month	Six Months	12 Months	p*
Hand grip strength (kgs)	Median IQR N	27.5 20.3-37.0 128	28.0 20.0-38.0 101	28.3 22.0-38.0 88	0.731
Male	Median IQR N	33.0 26.0-41.0 82	35.8 27.8-40.0 62	35.8 27.8-42.0 54	0.857
Female	Median IQR N	20 15.8-25.6 46	20 15.0-26.0 39	22 17.5-25.0 34	0.233

*Friedman's test

Figure 5.3 – Median hand grip strength scores (kgs)

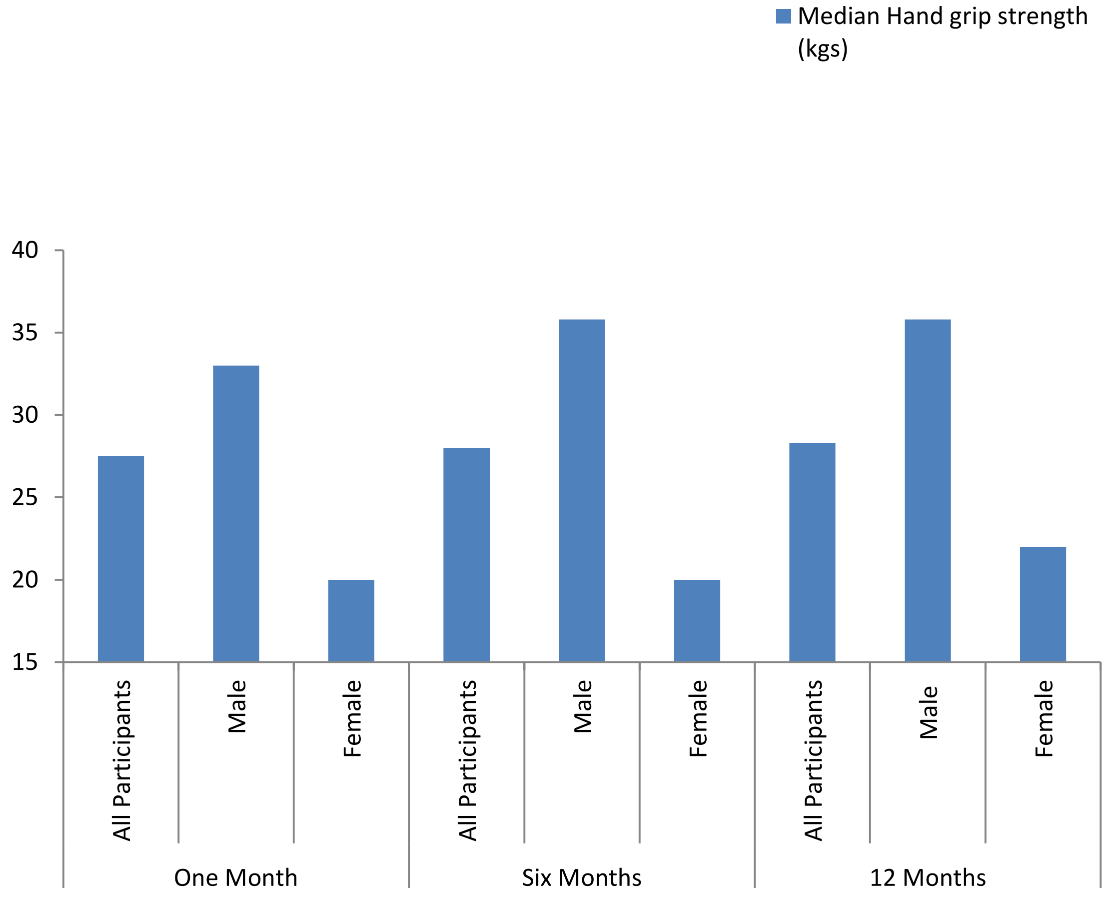


Table 5.5 - Leg strength scores at each time point

		One Month	Six Months	12 Months	p*
Leg strength (Newtons)	Median IQR N	265.4 222.9-330.1 66	279.3 221.0-341.4 53	292.4 221.4-346.9 44	0.212
Male	Median IQR N	292.9 239.9-333.3 42	297.9 244.3-341.4 33	312.2 264.3-350.4 27	0.102
Female	Median IQR N	243.5 188.7-309.3 24	261.5 191.2-343.1 20	245.2 186.8-307.6 17	0.444

*Friedman's test

Figure 5.4 – Median leg strength (Newtons)

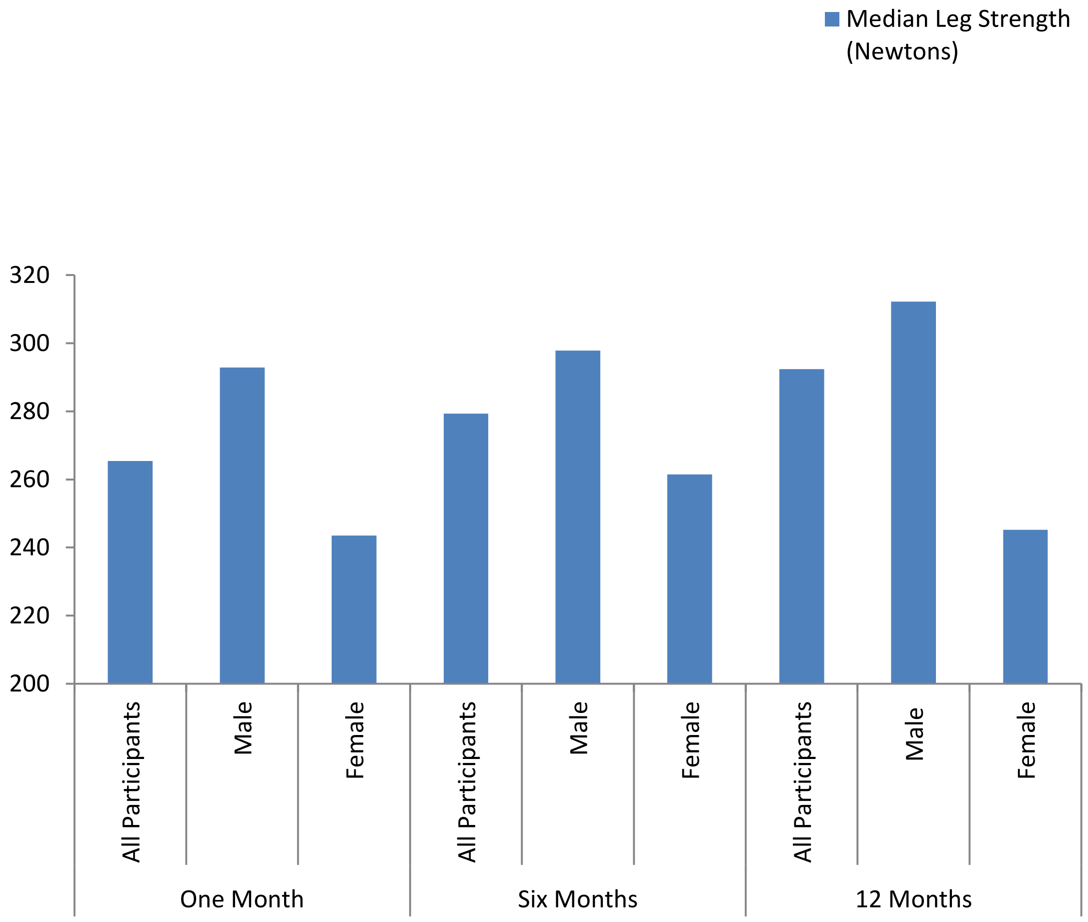


Table 5.6 - Leg extensor power scores at each time point

		One Month	Six Months	12 Months	p*
Leg power (Watts per kg)	Median IQR N	1.6 1.0-2.1 65	1.7 1.2-2.3 53	1.8 1.3-2.2 45	0.020
Male	Median IQR N	1.8 1.3-2.2 42	2.1 1.4-2.5 33	2.0 1.6-2.2 27	0.034
Female	Median IQR N	1.1 0.9-1.6 23	1.3 0.9-2.0 20	1.4 1.0-2.1 18	0.444

*Friedman's test

Figure 5.5 – Median leg power (watts per kg)

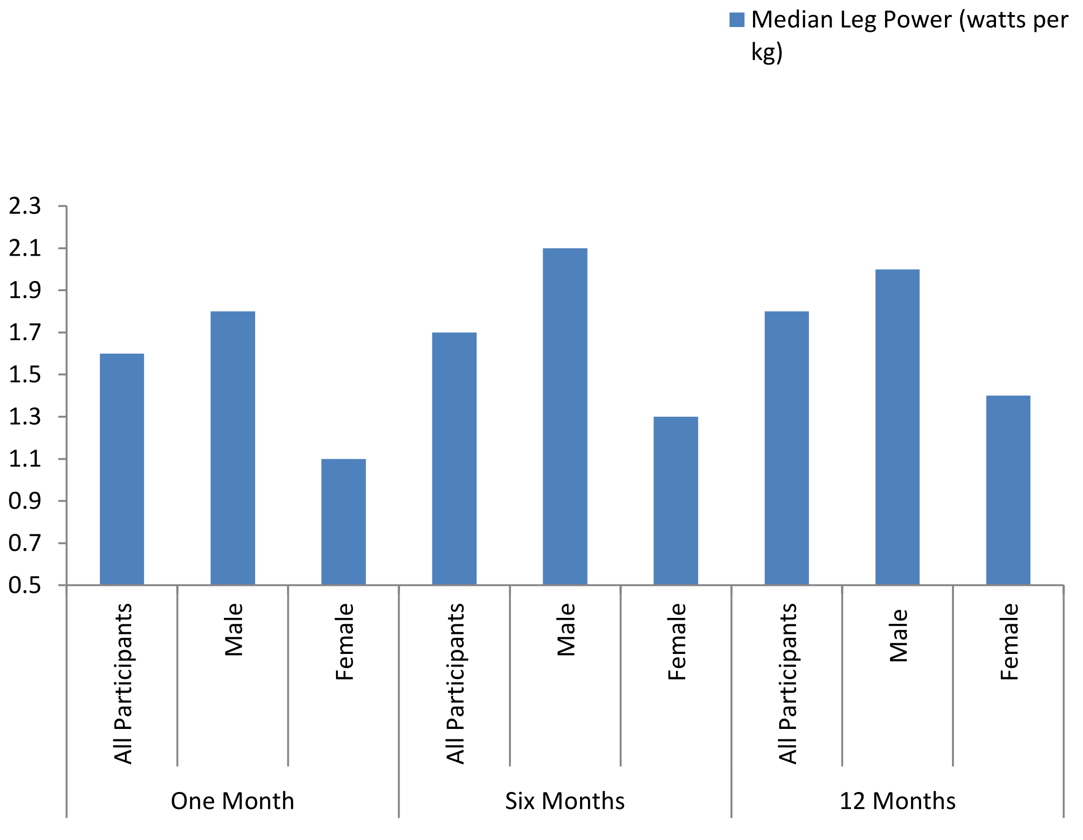
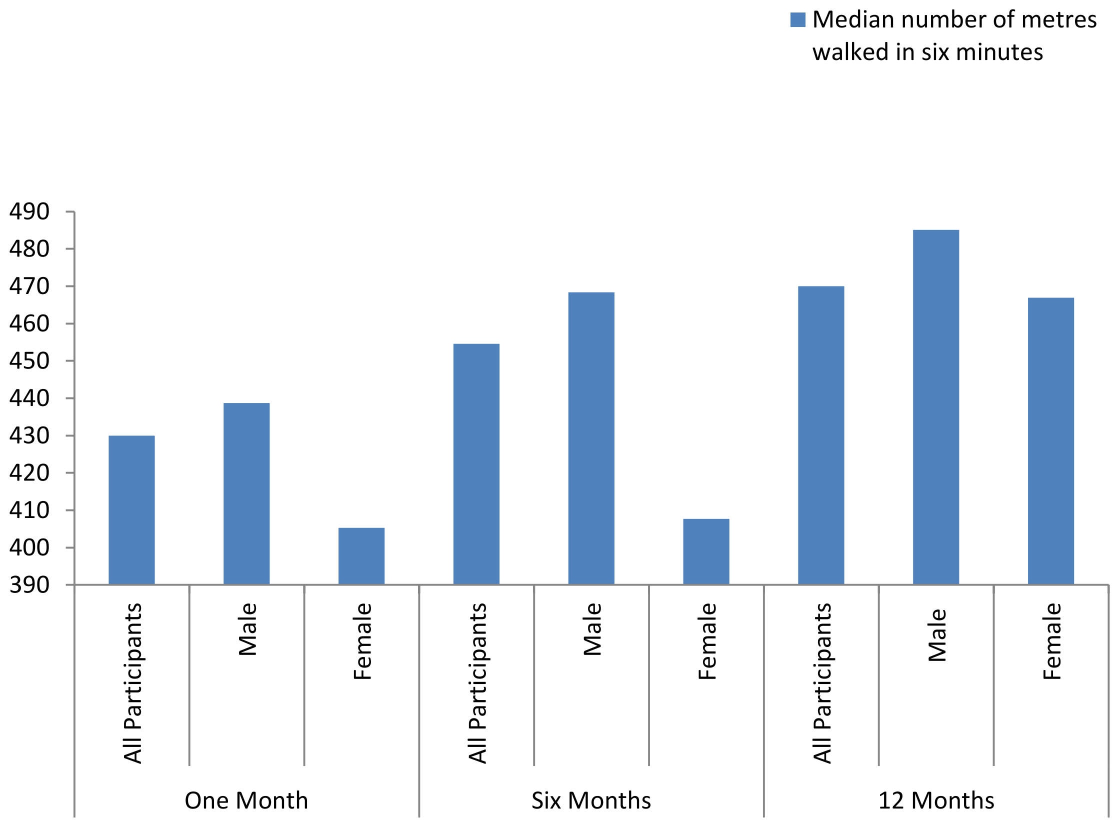


Table 5.7 - Distance walked in six minutes at each time point

		One Month	Six Months	12 Months	p*
Distance walked in six minutes (metres)	Median IQR N	430.0 339.0-491.8 58	454.6 314.8-497.3 46	470.0 427.3-515.0 34	<0.001
Male	Median IQR N	438.7 350.1-493.5 41	468.4 389.5-497.6 28	485.1 438.3-510.8 22	<0.001
Female	Median IQR N	405.3 313.5-492.5 17	407.7 253.9-511.4 18	466.9 404.9-555.5 12	0.004

*Friedman's test

Figure 5.6 – Median number of metres walked in six minutes



Uni-variate associations with fatigue

Uni-variate associations between baseline measures and fatigue at each time point

In this study, the term "baseline characteristics" or "baseline measures" refers to measures that were taken at either admission or at the time the participant was recruited to the study.

The uni-variate analysis revealed an inverse relationship between PASE scores and FAS scores at one month. Higher PASE scores (pre-stroke activity) at baseline are significantly related to lower log-transformed FAS scores at one month after stroke onset (p= 0.002). In other words, those participants who did more activity before their stroke tended to have lower fatigue severity at one month after stroke. None of the other measures taken at admission or recruitment were significantly associated with log-transformed FAS scores at the one month time point (Table 5.8)

An inverse relationship was also found between diastolic BP at baseline and fatigue severity at one month. Higher diastolic BP at baseline was significantly related to lower log-transformed FAS scores at six months after stroke onset (p=0.005). None of the other measures taken at admission or recruitment were significantly associated with log FAS scores at the six month time point (Table 5.8).

None of the measures taken at admission or recruitment were associated with log-transformed FAS scores at the 12 month time point (Table 5.8).

Table 5.8 - Associations between measures taken at admission or recruitment and log-transformed FAS scores at one, six and 12 months after stroke onset.(Spearman's correlations and Independent samples t-test)

Baseline Characteristic		Log-transformed FAS at one month	Log-transformed FAS at six months	Log-transformed FAS at 12 months
Age	Coefficient p-value	-0.045 0.611	-0.010 0.919	0.012 0.914
PASE Score	Coefficient p-value	-0.268 0.002**	-0.244 0.013	-0.261 0.013
BP (Systolic)	Coefficient p-value	-0.030 0.739	-0.048 0.634	-0.166 0.123
BP (Diastolic)	Coefficient p-value	-0.063 0.486	-0.281 0.005**	-0.203 0.059
NIHSS	Coefficient p-value	0.086 0.331	0.083 0.404	0.092 0.390
MMSE	Coefficient p-value	-0.119 0.202	0.090 0.388	-0.038 0.736
Social deprivation rank	Coefficient p-value	-0.192 0.027	-0.181 0.065	-0.083 0.433
Gender	T-test p-value	-1.44 0.150	-0.159 0.874	0.128 0.898
Pre-stroke fatigue	T-test p-value	0.496 0.621	2.012 0.047	2.117 0.037
Previous stroke	T-test p-value	1.554 0.123	1.439 0.153	1.914 0.059
History of hypertension	T-test p-value	-0.017 0.987	1.494 0.138	0.928 0.356
History of diabetes	T-test p-value	0.891 0.375	2.039 0.044	0.734 0.465
POCS diagnosis	T-test p-value	-2.365 0.020	0.465 0.643	0.901 0.370
Ischaemic or haemorrhagic	T-test p-value	-0.507 0.613	0.468 0.641	0.117 0.907
Side of lesion (left or right)	T-test p-value	-0.252 0.801	-0.011 0.991	0.075 0.940

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

None of the baseline measures were found to be significantly associated with clinically significant fatigue at any of the time points (Table 5.9).

Table 5.9 - Associations between baseline measures and clinically significant fatigue at one, six and 12 months after stroke onset.

Base-line Measure	One Month			Six Months			12 Months		
	Fatigued (n=43)	Not fatigued (n=89)	p-value	Fatigued (n=23)	Not fatigued (n=82)	p-value	Fatigued (n=18)	Not fatigued (n=73)	p-value
Age (Median, IQR)	68.4 (61.0-76.5)	72.1 (63.8-80.8)	0.304[a]	73.9 (64.8-81.4)	70.7 (64.1-78.4)	0.448[a]	73.4 (64.3-85.3)	70.3 (63.8-76.5)	0.213[a]
PASE Score (Median, IQR)	79.5 (59.0-135.5), n=42	106.0 (51.0-158.0)	0.339[a]	86.5 (50-121.5), n=22	103.5 (59.0-162.3)	0.173[a]	69 (50.5-117.0), n=17	114.0 (67.5-164.0)	0.042[a]
Systolic BP (Mean, SD)	141.7 (22.8), n=41	150.2 (28.2), n=84	0.095[b]	143.8 (20.5), n=21	149.7 (27.1), n=79	0.350[b]	144.9 (23.4), n=17	148.7 (26.7), n=70	0.592[b]
Dia-stolic BP (Mean, SD)	77.9 (14.4), n=41	80.5 (14.7), n=84	0.352[b]	75.8 (14.5), n=21	79.5 (14.1), n=79	0.281[b]	76.8 (14.7), n=17	79.4 (14.5), n= 70	0.515[b]
NIHSS (Median, IQR)	3 (1-4)	2 (1-3), n=87	0.201[a]	3 (1-4)	2 (1-4), n=80	0.513[a]	3 (1-5.3)	2 (1-3), n=71	0.072[a]
MMSE (Median, IQR)	27 (25-28.3), n=38	27 (25-29), n=79	0.719[a]	27 (25-28.5), n=21	27 (25-29), n=73	0.923[a]	28 (26-28.5), n=17	27 (25-29), n= 63	0.438[a]
Social Depriva-tion Rank (Median, IQR)	3280 (1588-5343)	4877 (2425-6140)	0.054[a]	3273 (2362-5015)	4783 (2406-6092)	0.127[a]	4226 (2420-5812)	4613 (2394-5989)	0.819[a]
Male (n, %)	17 (39.5)	30 (33.7)	0.563[c]	9 (39.1)	32 (39.0)	1.000[c]	4 (22.2)	31 (42.5)	0.176[c]
Pre-stroke fatigue (n, %)	19 (44.2)	37 (41.6)	0.852[c]	15 (65.2)	32 (39.0)	0.033[c]	11 (61.1)	32 (43.8)	0.202[c]
Previous stroke (n, %)	10 (23.3)	19 (21.3)	0.825[c]	8 (34.8)	15 (18.3)	0.151[c]	5 (27.8)	17 (23.3)	0.761[c]
History of hyper-tension (n, %)	19 (44.2)	49 (55.1)	0.269[c]	16 (69.6)	42 (51.2)	0.156[c]	14 (77.8)	33 (45.2)	0.017[c]
History of dia-betes	8 (18.6)	14 (15.7)	0.804[c]	7 (30.4)	11 (13.4)	0.067[c]	5 (27.8)	11 (15.1)	0.297[c]

(n, %)									
POCS diagnosis (n, %)	12 (27.9)	20 (22.5), n=88	0.523[c]	6 (26.1)	19 (23.2), n=81	0.787[c]	4 (22.2)	19 (26.0), n=72	1.000[c]
Ischae-mic stroke (n, %)	39 (90.7)	84 (94.4)	0.472[c]	22 (95.7)	77 (93.9)	0.752[c]	17 (94.4)	68 (93.2)	1.000[c]
Right lesion (n, %)	21 (58.3), n=36	45 (54.9), n= 82	0.841[c]	11 (50.0), n=22	37 (52.1), n=71	1.000[c]	8 (50.0), n =16	31 (49.2), n = 63	1.000[c]

a = Mann-Whitney U test

b = Independent samples t test

c = Fisher's exact test

Uni-variate associations between measures taken at one, six and 12 months and log-transformed FAS scores at the corresponding time point.

The uni-variate analysis revealed that the physical activity measures and the measures of anxiety, depression, sleepiness and quality of life (EuroQoL) at each time point were significantly associated with log-transformed FAS score at each corresponding time point. Lower levels of activity and quality life were associated with higher levels of fatigue. Higher levels of anxiety, depression and sleepiness were associated with higher fatigue severity (Table 5.10).

None of the fitness measures of hand grip strength, leg strength, leg power and distance walked in six minutes were significantly associated with log-transformed FAS score at any time point (Table 5.10). This was still the case when the scores for male and female participants were analysed separately on these measures.

Table 5.10 Spearman's correlations of log-transformed FAS with recorded characteristics at individual time points.

Characteristic recorded at one, six and 12 months		Log-transformed FAS score at one month	Log-transformed FAS score at six months	Log-transformed FAS score at 12 months
Time spent sitting or lying on average per day	Coefficient p-value N	0.349 0.001** 84	0.189 0.120 69	0.231 0.084 57
Time spent upright on average per day	Coefficient p-value N	-0.310 0.004** 84	-0.087 0.475 69	-0.098 0.466 57
Time spent stepping on average per day	Coefficient p-value N	-0.392 0.000** 84	-0.312 0.009** 69	-0.369 0.005** 57
Steps taken on average per day	Coefficient p-value N	-0.393 0.000** 84	-0.305 0.011 69	-0.360 0.006** 57
Distance walked in six minutes	Coefficient p-value N	-0.137 0.304 58	-0.334 0.023 46	-0.100 0.574 34
Leg power of non-affected side	Coefficient p-value N	-0.070 0.581 65	-0.081 0.565 53	-0.057 0.710 45
Leg strength of non-affected side	Coefficient p-value N	0.134 0.283 66	-0.115 0.412 53	0.122 0.429 44
Hand grip strength of non-affected side	Coefficient p-value N	-0.181 0.040 128	-0.217 0.029 101	-0.135 0.209 88
Anxiety (HADS)	Coefficient p-value N	0.496 0.000** 132	0.524 0.000** 105	0.588 0.000** 91
Depression (HADS)	Coefficient p-value N	0.531 0.000** 132	0.592 0.000** 105	0.588 0.000** 91
Sleepiness (Epworth sleepiness scale)	Coefficient p-value N	0.400 0.000** 132	0.414 0.000** 105	0.514 0.000** 91
Quality of Life (EuroQoL)	Coefficient p-value N	-0.494 0.000** 132	-0.544 0.000** 105	-0.607 0.000** 91

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

At the one month time point, participants who were fatigued (according to case definition) had significantly higher depression and sleepiness scores and significantly lower quality of life scores than participants who were not fatigued (Table 5.11).

At the six month time point, fatigued participants spent significantly less time stepping and did significantly fewer steps on average per day than participants who were not fatigued. Fatigued participants also had significantly higher depression and sleepiness scores and lower quality of life scores (Table 5.12).

At the 12 month time point, fatigued participants spent significantly less time stepping and had significantly lower quality of life scores than non-fatigued participants (Table 5.13).

Table 5.11 - Relationship between recorded characteristics and case definition at one month

Characteristic	**Fatigued** Median IQR N	**Not fatigued** Median IQR N	Mann-Whitney U p-value
Time spent sitting or lying on average per day (hours)	20.5 18.5-22.3 24	20.0 18.3-22.1 60	633.0 0.389
Time spent upright on average per day (hours)	2.5 1.3-4.6 24	3.1 1.5-4.6 60	787.0 0.507
Time spent stepping on average per day (hours)	0.6 0.2-1.0 24	0.8 0.4-1.3 60	888.5 0.095
Steps taken on average per day (thousands)	2483.9 798.4-4545.3 24	3424.2 1637.3-5947.1 60	888.0 0.096
Leg strength of non-affected side (Newtons)	267.1 214.7-339.1 16	265.4 222.9-328.9 50	387.0 0.846
Leg power of non-affected side (Watts per kg)	1.6 0.9-2.1 16	1.5 1.0-2.1 49	416.0 0.715
Hand grip strength of non-affected side (kgs)	26.0 18.0-33.0 43	29.0 22.0-40.0 85	2162.0 0.091
Distance walked in six minutes (metres)	432.0 342.7-498.6 13	428.0 338.7-493.5 45	297.5 0.926
Anxiety (HADS)	7.0 3.0-12.0 43	6.0 3.0-8.0 89	1552.5 0.079
Depression (HADS)	8.0 5.0-9.0 43	4.0 2.0-7.5 89	1181.0 ≤0.0001**
Sleepiness (Epworth sleepiness scale)	9.0 5.0-15.0 43	6.0 3.5-10.0 89	1365.0 0.008**
Quality of Life (EuroQoL)	0.6 0.2-0.7 43	0.7 0.6-0.9 89	2608.0 0.001**

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

Table 5.12 - Relationship between recorded characteristics and case definition at six months

Characteristic	**Fatigued** Median IQR N	**Not fatigued** Median IQR N	Mann-Whitney U p-value
Time spent sitting or lying on average per day (hours)	20.7 18.8-21.5 14	18.9 17.9-20.2 55	273.0 0.095
Time spent upright on average per day (hours)	2.9 2.1-4.3 14	3.9 2.7-5.0 55	454.0 0.303
Time spent stepping on average per day (hours)	0.5 0.2-0.9 14	1.0 0.5-1.5 55	556.5 0.010**
Steps taken on average per day (thousands)	2315.8 868.9-3647.0 14	4617.3 2401.6-7294.7 55	1318.5 0.003**
Leg strength of non-affected side (Newtons)	279.3 236.9-364.3 9	279.1 204.7-339.6 44	189.0 0.843
Leg power of non-affected side (Watts per kg)	1.4 1.0-2.5 9	1.8 1.3-2.3 44	218.0 0.650
Hand grip strength of non-affected side (kgs)	26.0 17.0-37.0 21	28.0 20.3-38.8 80	948.5 0.364
Distance walked in six minutes (metres)	416.2 216.1-469.8 6	455.4 330.6-508.6 40	159.0 0.215
Anxiety (HADS)	7.0 4.0-13.0 23	4.0 2.0-7.0 82	626.5 0.014
Depression (HADS)	6.0 3.0-12.0 23	4.0 1.0-7.0 82	613.5 0.010**
Sleepiness (Epworth sleepiness scale)	9.0 5.0-15.0 23	5.0 2.0-9.0 82	606.0 0.009**
Quality of Life (EuroQoL)	0.6 0.1-0.8 23	0.8 0.6-1.0 82	1318.5 0.003**

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

Table 5.13 - Relationship between recorded characteristics and case definition at 12 months

Characteristic	**Fatigued** Median IQR N	**Not fatigued** Median IQR N	Mann-Whitney U p-value
Time spent sitting or lying on average per day (hours)	21.2 19.1-22.9 11	19.3 17.2-20.3 46	143.5 0.027
Time spent upright on average per day (hours)	2.1 0.9-4.2 11	3.5 3.0-5.2 46	342.0 0.072
Time spent stepping on average per day (hours)	0.6 0.2-0.7 11	1.1 0.7-1.5 46	388.0 0.006**
Steps taken on average per day (hours)	2637.3 532.0-3391.7 11	4952.0 2977.2-7601.8 46	379.0 0.011
Leg strength of non-affected side (Newtons)	335.8 211.2-378.1 5	291.7 225.4-345.0 39	79.0 0.517
Leg power of non-affected side (Watts per kg)	1.8 1.2-2.6 5	1.8 1.3-2.2 40	91.0 0.766
Hand grip strength of non-affected side (kgs)	24.0 21.5-35.5 17	29.0 23.0-41.0 71	698.0 0.318
Distance walked in six minutes (metres)	457.4 N/A 3	470.4 428.0-527.5 31	57.5 0.524
Anxiety (HADS)	7.0 4.0-11.3 18	5.0 2.0-7.0 73	425.0 0.020
Depression (HADS)	5.5 3.0-10.5 18	4.0 2.0-6.0 73	415.0 0.015
Sleepiness (Epworth sleepiness scale)	10.0 2.5-15.0 18	4.0 2.0-8.0 73	464.5 0.054
Quality of Life (EuroQoL)	0.6 0.01-0.7 18	0.8 0.6-0.9 73	1029.0 ≤0.000**

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

Multi-variate analysis

Logistic Regression

A logistic regression analysis was planned to investigate which baseline and one month assessment characteristics are predictors of the presence or absence of clinically significant fatigue at later time points as measured by the case definition. However there was an insufficient number of participants fulfilling the case definition at the six and 12 month time points for this analysis to be performed.

Linear Regression

EM Imputation

Little's MCAR test for EM estimated statistics was not significant (Chi-square = 7.6, p = 0.471) indicating that the data were missing completely at random.

Replacing the missing values increased the number of valid total FAS scores from 105 to up to 136 at six months and from 91 to up to 136 at 12 months and consequently increased the cases of valid activity data from 67 to 84 at six months and from 57 to 84 at 12 months.

A uni-variate analysis revealed that PASE scores and the one month variables time spent stepping on average per day, average number of steps taken per day, anxiety, depression, sleepiness and quality of life are all significantly related to log-transformed FAS total scores with missing answers imputed at both six and 12 months (Table 5.14). Therefore these variables were identified as being potential independent variables for the regression models.

Spearman's correlations between all these potential variables were then examined to ensure that they were not too highly correlated with each other (Appendix 17). The variables time spent stepping and steps taken on average per day were very highly correlated with each other (p=0.993), therefore only steps per day were included in the regression models to avoid the assumption of no multi-collinearity in the data being violated. Steps per day were chosen to be included in the regression models instead of time spent stepping as step count has been reported in several studies of physical activity after stroke (Field et al. 2013). No other combination of independent variables had a correlation of 0.8 or above.

Table 5.14 - Spearman's correlations between characteristics recorded at baseline, recruitment or at the one month assessment and log-transformed FAS score with missing answers imputed at the six and 12 month time points.

Characteristic recorded at baseline, recruitment or at the one month assessment		Log-transformed FAS total score at six months with missing values imputed	Log-transformed FAS total score at 12 months with missing values imputed
PASE	Coefficient p-value N	-0.292 0.001 135	-0.302 <0.0001 135
Time spent stepping on average per day	Coefficient p-value N	-0.391 <0.0001 84	-0.312 0.004 84
Steps taken on average per day	Coefficient p-value N	-0.406 <0.0001 84	-0.333 0.002 84
Anxiety (HADS)	Coefficient p-value N	0.407 <0.0001 132	0.381 <0.0001 132
Depression (HADS)	Coefficient p-value N	0.321 <0.0001 132	0.345 <0.0001 132
Sleepiness (Epworth sleepiness scale)	Coefficient p-value N	0.329 <0.0001 132	0.316 <0.0001 132
Quality of Life (EuroQoL)	Coefficient p-value N	-0.357 <0.0001 132	-0.323 <0.0001 132
Log-transformed FAS total score at one month	Coefficient p-value N	0.585 <0.0001 132	0.644 <0.0001 132

The final regression models for the six and 12 month time points were very similar to each other. The hierarchical exploratory approach produced a significant model at both time points ($F(5,78) = 7.136$ at six months, $F(5,78) = 5.724$ at 12 months, $p < 0.0001$ at both time points). The model for the six month time point explains 27% of the variance (Adjusted R square = 0.270) and the model for the 12 month time point explains 22.2% of the variance (Adjusted R Square = 0.222). In both models lower levels of physical activity as measured by the variable average number of steps taken per day at one month were significantly associated with higher levels of fatigue even when age, gender, fatigue before stroke and anxiety had been taken into account. Anxiety at one month was also found to be a significant independent predictor of log-transformed FAS score at each time point. Further information about the variables in each model are shown in Tables 5.15 and 5.16.

The Adjusted R square values have been reported as these values give more of an indication of how well these models can be generalised to the population that is being studied than the R square value (Field 2005).

Assumptions of regression

All the assumptions of regression were met. The VIF values in both the regression models were well below 10 (mean VIF value of 1.1 for both models) and the tolerance statistics were all well above 0.2 (mean tolerance of 0.9 for both models) therefore it can be concluded that there is no collinearity within our data (Field 2005).

Neither of the regression models had a Durbin-Watson value of less than one or more than three (2.3 at six months and 2.1 at 12 months) so it can be concluded that the residuals in the models were independent (Field 2005).

Examining histograms and Normal P-P Plots that the SPSS output produced revealed that the residuals in both regression models were normally distributed.

Examining the scatterplots of standardised residuals against standardised predicted values which were produced by the SPSS output revealed that the assumptions of linearity and homoscedasticity were met.

Table 5.15 - Multiple Linear Regression Model: Predictors of log-transformed FAS at six months post-stroke

Measured characteristic	B	SE B	Beta	p
Average number of steps taken per day at one month	-1.217E-5	<0.0001	-0.316	0.002
Anxiety at one month	0.014	0.003	0.443	<0.0001
Fatigue before stroke onset	-0.013	0.025	-0.051	0.600
Gender of participant	0.013	0.027	0.048	0.633
Age of participant	<0.0001	0.001	0.029	0.769

Table 5.16 - Multiple Linear Regression Model: Predictors of log-transformed FAS at 12 months post-stroke.

Variable	B	SE B	Beta	p
Average number of steps taken per day at one month	-1.231E-5	<0.0001	-0.285	0.006
Anxiety at one month	0.014	0.004	0.398	<0.0001
Fatigue before stroke onset	-0.031	0.029	-0.106	0.297
Gender of participant	-0.005	0.032	-0.017	0.868
Age of participant	0.001	0.001	0.100	0.337

Alternative models and sensitivity analyses

When the analyses for the six and 12 month models were re-run with the variable depression included, the models had a slightly poorer fit ($F(6,77) = 5.875$, Adjusted R Square = 0.261 at six months and $F(6,77) = 4.722$ Adjusted R Square = 0.212 at 12 months) and depression was not found to be a significant predictor of log-transformed FAS score in either model whereas anxiety and average number of steps taken per day remained significant predictors.

When the variable PASE scores was included in each model the models had a slightly better fit ($F(6,76) = 6.206$, Adjusted R square = 0.276 at six months and $F(6,76) = 5.016$, Adjusted R Square = 0.227 at 12 months). The variable anxiety remained a significant predictor in both models but steps taken per day was no longer a significant predictor. However PASE score was not found to be a significant predictor of log-transformed FAS score in either model and examining the beta values revealed that steps taken per day was a more important predictor of log-transformed FAS score than PASE scores.

Excluding the variables age, gender and fatigue before stroke onset from both models resulted in each model having a slightly better fit to the FAS data ($F(2,81) = 17.945$, Adjusted R Square = 0.290) at six months and $F(2,81) = 13.418$, Adjusted R Square = 0.230 at 12 months). The variables anxiety and number of steps taken per day remained significant predictor of log-transformed FAS scores.

Re-running the analyses with log-transformed FAS score at one month as an independent variable resulted in better fitting models at both six and 12 months

($F(6,77) = 9.345$, Adjusted R Square = 0.376 at six months, $F(6,77) = 8.780$, Adjusted R Square = 0.360 at 12 months). The variables anxiety and steps taken per day were no longer significant predictors of six or 12 month log-transformed FAS score. Log-transformed FAS score at one month was a significant predictor of log-transformed FAS score at six months and log-transformed FAS score at 12 months ($p<0.0001$ at both time points).

Re-running the analyses using the log-transformed FAS scores without the missing values imputed resulted in very similar models. For the six month model the Adjusted R square was slightly bigger than the equivalent model with missing values imputed (0.284) and the F value was slightly smaller ($F(5,61) = 6.248$). The variables anxiety and steps taken per day remained significant predictors ($p<0.0001$ and $p = 0.007$). For the 12 month model the Adjusted R square was slightly less than the equivalent model with missing values imputed (0.21) and the F value is slightly smaller ($F(5,52) = 4.027$. The variable anxiety remained a significant predictor ($p = 0.003$) however average number of steps per day was no longer a significant predictor ($p = 0.037$).

Discussion

This is the first study to investigate the relationship between fatigue after stroke and physical activity and/or fitness using a longitudinal design.

Physical activity after stroke

The participants in this study took a similar number of steps per day as was reported in a recent meta-analysis of step counts after stroke (Field et al. 2013) and took a lower number of steps per day than would be expected in an age-matched healthy population (Tudor-Locke et al. 2002). Leg power, leg strength, hand grip strength and six minute walk scores and mean daily step counts for healthy adults are presented in appendices 18-21 (Skelton et al. 1994; Bohannon 2006; Bohannon 2007; Field et al. 2013). A comparison of these normative values with the values obtained by the participants in this study indicates that on average the latter have lower levels of fitness than healthy adults in a similar age group.

This study found that there was a significant relationship between step count and fatigue. Participants with clinically significant fatigue took a significantly lower number of steps per day than participants without clinically significant fatigue. This was the case at all three time points. Participants with higher log-transformed FAS scores were significantly more likely to have a lower daily step count at each of the three time points. This finding is consistent with Robinson et al. (2011) who also reported that a lower number of steps taken per day to be significantly associated with higher fatigue levels. This finding is not consistent with two previous studies which reported that daily step count was not associated with fatigue after stroke (Michael, & Macko 2007; Michael, Allen & Macko 2006).

However these two studies only measured activity for a period of 48 hours which means they may not have obtained such a precise estimate of step count as Robinson et al. (2011) or the current study which both aimed to measure activity over seven days.

The multivariate analysis revealed that daily step count at one month is an independent significant predictor of log-transformed FAS score at six and 12 months after stroke even when age, gender, pre-stroke fatigue and anxiety were taken into account. These regression models accounted for 27% and 22% of the variance in log-transformed FAS scores at six and 12 months respectively indicating that there are still other factors which contribute to log-transformed FAS score at six and 12 months after stroke. Anxiety at one month was also found to be an independent significant predictor of log-transformed FAS score at six and 12 months. Anxiety at one month was found to be a more important predictor than physical activity whereas, interestingly, depression at one month was not found to be a significant predictor of log-transformed FAS score at six or 12 months. This is interesting as a recent meta-analysis of studies which investigated the psychosocial associations of fatigue after stroke reported depressive symptoms to be statistically significantly associated with fatigue after stroke but there was only a "trend" towards a significant relationship between anxiety and fatigue after stroke (Wu et al. 2014, p1781).

Unfortunately the design of this study does not provide definitive evidence regarding the direction of the relationship between low activity and higher fatigue. In other words, it cannot prove that low activity and higher anxiety at one month cause higher fatigue severity scores at six and 12 months, only that there is an association. Generally, even though longitudinal designs cannot prove causal inferences they can potentially provide information regarding the direction of relationships as they can provide the opportunity to rule out alternative explanations which are not possible or plausible. For instance, it is not possible that fatigue at six or 12 months causes low activity at one month. However in the case of this study the longitudinal design cannot rule out the plausible explanation that fatigue at one month causes stroke survivors to do less activity or have higher anxiety levels at one month and this fatigue at one month also influences their fatigue severity scores at the six and 12 months time points.

This alternative explanation has some support from this study in that when the variable log-transformed FAS score at one month was entered into the regression model as an independent variable it was found to be a significant predictor of log-transformed FAS score at six and 12 months post-stroke whereas activity and anxiety were no longer significant predictors. Moreover this explanation is consistent with the findings of Lerdal and Gay (2013) who reported that the presence of fatigue two weeks post-stroke was the best predictor of fatigue at 18 months post-stroke even when physical health, depression and sociodemographic variables were taken into account (Lerdal & Gay 2013). However it is still also plausible that low levels of activity and/or high levels of anxiety at one month may cause high fatigue severity scores at one month and these high fatigue severity scores at one month are what causes high fatigue severity scores at six and 12 months. In other words, anxiety and activity may have an indirect influence on fatigue severity scores at six and 12 months through the third variable of fatigue severity score at one month.

It is also possible that there is not a direct relationship between activity and/or anxiety and fatigue at all. There could be another unknown variable which causes low activity, high anxiety and high fatigue. For instance, one of the studies identified in the systematic review in Chapter 3 carried out a Structural Equation Modelling (SEM) analysis to attempt to understand the direction of relationships between variables and reported that fatigue severity "indirectly influenced the amount of exercise a stroke survivor did through their self-efficacy expectations" (Shaughnessy, Resnick and Macko 2006, p17).

The best source of evidence that one variable actually causes another is by carrying out a randomised controlled trial (RCT). Numerous RCTs have been carried out in people with CFS, MS and cancer and have reported that exercise training either has no effect on fatigue (i.e. does not cause further fatigue) or, in most cases, effectively reduces fatigue (Larun et al. 2015; Latimer-Cheung et al. 2013; Pilutti et al. 2013; Molt and Pilutti 2012; Amato and Portaccio 2012; Puetz and Herring 2012; Brown et al. 2011; McMillan and Newhouse 2011). In the stroke literature, one RCT reported that fatigue levels significantly reduced when exercise training was used in combination with CBT (Zedlitz et al. 2012) and another RCT reported that a programme of circuit training did not result in higher fatigue levels as compared to usual physiotherapy treatment (van de Port et al. 2012) suggesting that the increased activity did not cause these stroke survivors to have more fatigue.

Fitness

The leg strength, leg power and hand grip scores in this study's sample were on average lower than have been previously reported in age-matched healthy population (Bohannon 2007; Bohannon 2006; Skelton et al. 1994) suggesting that the participants in this study may have experienced some de-conditioning. However, none of the measures of physical fitness that were taken in this study were found to be significantly related to fatigue severity or to the presence of clinically significant fatigue. This lack of an association between physical fitness and fatigue is consistent with the studies identified in Chapter 3. Six of these studies investigated whether fatigue was associated with at least one measure of physical fitness but only one reported a significant association. Lewis et al. (2011) reported a relationship between higher levels of lower limb extensor power and lower levels of fatigue. Across the other five studies no associations were reported between fatigue and peak exercise capacity (Tseng et al. 2010; Michael and Macko 2007; Michael, Allen and Macko 2006), the 10 meter walk test or the six minute walk test (Miller et al. 2013; Hoang et al. 2012).

Measures taken at admission and recruitment

The baseline measure which was the most consistently associated with log-transformed FAS score was the measure of pre-stroke activity levels (significantly associated at one month and very nearly significantly associated at six and 12 months post stroke). This is an interesting finding as it implies that a possible way of reducing the number of people who are fatigued after a stroke would be to encourage healthy people to stay as active as possible. However, when PASE scores were added into the regression model they did not significantly predict FAS scores at six or 12 months whereas the number of steps taken per day at one month was still a significant predictor and had a larger beta value suggesting that post-stroke activity is a better predictor of fatigue severity at six and 12 months than pre-stroke activity.

Moreover the only two previous studies to have investigated the relationship between pre-stroke activity and post-stroke fatigue found no association between these two measures (Shaughnessy, Resnick & Macko 2006; Choi-Kwon et al. 2005). Therefore, currently there is not strong evidence for the idea that increasing activity levels may be a strategy for a person to protect themselves against getting fatigue should they ever have a stroke.

A significant association was also found between higher levels of diastolic blood pressure at admission and lower levels of fatigue severity at the six month time point. None of the other measures taken at baseline or recruitment were found to be significantly associated with fatigue severity or clinically significant fatigue. These results suggest that a clinician is unlikely to be able to predict fatigue severity levels or who will develop clinically significant fatigue by measuring the patient characteristics that were recorded in this study at baseline or recruitment.

Strengths of Study

This study has several strengths. Most of the measurements of baseline variables were taken directly from clinical records. It is the first study to explore the relationship between pre-stroke activity levels and post-stroke fatigue using an instrument which has been tested for validity and reliability and has been previously used in research with stroke patients.

A major strength of this study is that physical activity was measured objectively using the ActivPAL™ accelerometer as opposed to using a subjective self-report questionnaire. Therefore it is the largest longitudinal study of fatigue and objectively measured activity which has been carried out in stroke patients. Another strength of the study is that several aspects of physical fitness were objectively measured and that the methods of measuring these aspects of fitness had all previously been used in studies of stroke patients.

Limitations of Study

The study had several limitations. For instance, participants who requested to complete a follow-up assessment in their own homes or in a rehabilitation hospital were unable to undertake the leg strength, leg power and six minute walk fitness tests as the equipment or facilities required for these tests were not portable. Potentially, these participants were in poorer health or had less motivation than those who did travel to the research facility, and this could have created a source of bias in the fitness data. Indeed the most common reasons expressed by participants for requesting a home visit were lack of mobility, lack of perceived mobility (i.e. not confident enough to leave house), feeling unwell or they felt that they lived too far away and this reduced their motivation to take a taxi to the hospital. The lack of portability of these tests potentially means that we were unable to find a statistically significant relationship between these fitness measures and fatigue because our sample size was too small. However we were able to get hand grip strength scores from all participants and still did not find a statistically significant relationship between hand grip strength and fatigue. Future research should use portable leg strength and leg power measuring instruments which could be taken to people's homes so that it is possible to obtain these measurements for a greater number of participants.

Another limitation of this study is that the methods of measuring physical fitness are all dependent on the participant trying their hardest. It is possible that some participants may not have walked as fast as they could in the 6MWT or pushed as hard as they could in the leg strength test meaning that their fitness levels may have been underestimated. However, most of the participants did seem to be genuinely motivated to do well in these tests so it is unlikely this is the case.

Another potential limitation of using the 6MWT as a measure of aerobic fitness is that it could be influenced by other factors which are not related to cardio-respiratory mechanisms. For instance, it is highly plausible that the 6MWT was effected by participants' confidence levels in their ability to walk after having a stroke. Some participants may have walked much slower than they were aerobically capable of because they were concerned that they may have a fall. This may explain why participants walked a longer distance at the six and 12 month assessments than the one month assessment as their confidence levels may have increased at the later time points.

One limitation of this study was the method of assessing pre-stroke fatigue. Pre-stroke fatigue was only assessed by asking participants at time of recruitment a single question requiring a Yes/No response; "Did you have a problem with fatigue before your stroke?" This question could have been subject to a recall bias or it could be argued that this single question is not an adequate measure of pre-stroke fatigue and instead the case definition for clinically significant fatigue should have been used at recruitment. As a result of not using a more thorough method of measuring pre-stroke fatigue, it cannot be determined from this study whether the fatigue that participants reported they had before their stroke was clinically significant or even if it had any characteristics in common with post-stroke fatigue at all. Indeed, participants in one qualitative study did report that their post-stroke fatigue was qualitatively different from any fatigue they had felt before (Roding et al. 2003). However, as only two other studies (Lerdal et al. 2011; Choi-Kwon et al. 2005) have even attempted to investigate the relationship between pre-stroke fatigue and post-stroke fatigue it could be considered a strength of the study that pre-stroke fatigue was assessed at all.

Additional limitations are that NIHSS scores were higher in participants who did not provide activity data. Stroke severity may confound the relationship between fatigue and inactivity which means it may not be possible to generalise the results of this study to the whole stroke population. Only 18 participants had clinically significant fatigue at 12 months which means that comparisons between those with and without clinically significant fatigue at this time point should be treated with caution and finally it should also be taken into consideration that two of the ten items of the FAS scale ("I don't do much during the day" and "I feel no desire to do anything") may be correlated with activity.

Collecting activity data by using the ActivPAL™

Activity data were collected for only approximately two-thirds of participants at each time point. The main reason for not being able to collect activity data from all participants was non-compliance. A number of participants refused to wear the ActivPAL™ at the time they were first asked to and a number of participants initially agreed to wear the ActivPAL™ but it was subsequently returned to the researcher without sufficient data recorded on it.

The reasons given for refusing to wear the ActivPAL™ from the start included concerns that ActivPAL™ might interfere with pacemaker, concerns that ActivPAL™ might fall off and that bending down to pick it up again would not be possible and a few participants expressed that they simply considered the request to wear an ActivPAL™ to be insensitive as they had recently completely lost their ability to walk due to their stroke.

There were a variety of reasons given to explain why a returned ActivPAL™ did not have sufficient data recorded on it. For instance a couple of participants reported that they had to remove it due to skin irritation and several participants reported that the ActivPAL™ had kept falling off and they had been unable to reattach it themselves. Some participants expressed that they were not psychologically comfortable with wearing the ActivPAL™. For instance, one participant removed it as she felt it was making her restless leg syndrome worse, another expressed she was becoming obsessed with watching the ActivPAL's™ flashing green light, another participant was concerned that it was recording his voice, and another participant returned the ActivPAL™ with a note that said "I'm sorry but I cannot cope with this right now". All of these participants attended all three assessments which suggests that it was specifically the ActivPAL™ that they had a problem with rather than the research study in general.

Participants not wearing accelerometers as instructed by researchers is a common issue in physical activity studies (Lee, Macfarlane & Lam 2013). The compliance rate in this study was substantially higher than has been previously reported (Trioano et al. 2008). Consequently a handful of recent studies have investigated whether people who are non-compliant share certain demographic, health or lifestyle characteristics. These studies have reported that non-compliance is associated with younger age (Lee, Macfarlane & Lam 2013; Roth & Mindell 2012), smoking (Lee, Macfarlane & Lam 2013; Roth & Mindell 2012), not being in full time paid employment (Roth & Mindell 2012), having a lower annual income (Gemmill et al. 2011), having a lower level of education (Lee, Macfarlane & Lam 2013; Gemmill et al. 2011), high self-reported health status (Lee, Macfarlane & Lam 2013), higher MMSE score and higher instrumental activities of daily living (IADL) score (Gemmill et al. 2011). The results of these studies are concerning as if these groups of people are consistently not providing activity data with accelerometers then this could lead to biases in this type of research. In the study reported in this chapter higher NIHSS was associated with non-compliance suggesting that the physical activity data are not representative of people with more severe strokes. However this was the only baseline characteristic in this study to be associated with ActivPAL™

non-compliance. Participants who were non-compliant with the ActivPAL™ had slightly higher anxiety and depression scores than those who were compliant but this difference was not statistically significant.

It was suspected that a number of ActivPALs™ had been lost in the post (n = 14) as the participants reported that they had posted it back to the researcher as requested but it failed to arrive. On a few occasions, the ActivPAL™ did not record any data due to technical problems and the participant refused to wear it for a second time.

It should also be taken into account that although the ActivPAL™ accelerometers are very accurate at measuring the number of steps a participant takes, they cannot measure all activity that a participant does. For instance, it cannot tell us if a participant has been taking part in a sport such as cycling, swimming or curling or what proportion of steps per day are taken walking up a steep hill which requires greater energy as opposed to flat ground. In addition, if a participant is in a wheelchair and uses their arms to push the chair, the ActivPAL™ would not be able to record this activity. The ActivPAL™ may also undercount steps in participants with slow or shuffling gaits (Storm, Heller and Mazza 2015). It is also possible that the Hawthorn Effect is taking place i.e. participants are doing many more steps than they normally would because the presence of the ActivPAL™ made them feel they were being evaluated (Gale 2004). However it is unlikely that the presence of the ActivPAL™ would affect a participant's activity levels after the first few days at the most (MacMillan & Kirk 2010).

Despite the limitations of the ActivPAL™, activity data were obtained from most of the participants which means that it should still be considered to be a feasible instrument for use with stroke patients. Future research should consider ways of improving the compliance rate. For instance financial reward per day that accelerometer was worn for or reminder phone calls (Sirard and Slater 2009). Future research should consider asking participants to keep an activity diary so that more information can be obtained about what kind of activities they do throughout the week. For instance, do they engage in activities which also offer social benefits or activities which help the participant to maintain their independence. There is also some evidence that keeping a diary may improve accelerometer compliance rates (Sirard and Slater 2009).

Conclusions

In conclusion, the stroke survivors in this study took a lower number of steps per day and had lower levels of physical fitness than would be expected in an age-matched healthy population. Lower levels of physical activity were associated with fatigue at each of the time points. Levels of physical fitness were not associated with fatigue at any of the time points. Lower levels of physical activity and higher levels of anxiety at one month were significant predictors of fatigue severity at six and 12 months post-stroke. Potential explanations for these findings will be discussed in Chapter 6.

Summary of Chapter 5

Background and aims

- The aetiology of fatigue after stroke is still unclear. This study aimed to investigate whether reduced physical activity and/or reduced physical fitness is associated with post-stroke fatigue.

Method

- Participants were assessed at one, six and 12 months after stroke onset. Physical activity was measured by using an accelerometer called an ActivPAL™. The ActivPAL™ records how much time a participant spends sitting or lying, how much time they spend standing, how much time they spent stepping and how many steps they take. Physical fitness was determined by measuring hand grip strength, lower limb extensor strength, lower limb extensor power and distance walked in six minutes. Fatigue severity was assessed by using the Fatigue Assessment Scale (FAS) and clinically significant fatigue was assessed by using an interview based case definition. Measures were taken of a variety of characteristics at baseline or recruitment.

Results

- At six and 12 months, a positive fatigue case definition was associated with lower amounts of physical activity. At one, six and 12 months, higher FAS (more fatigue) was associated with lower amounts of physical activity, higher depression, anxiety scores and sleepiness and poorer quality of life. Lower amounts of physical activity and greater anxiety at one month independently predicted higher FAS at six and 12 months.

- Higher PASE scores at one month and higher diastolic BP at six months were negatively correlated with FAS scores and were the only measures taken at baseline or recruitment that were found to be significantly associated with FAS score. None of the measures taken at baseline or recruitment were found to be significantly associated with a positive fatigue case definition.
- None of the fitness measures were found to be significantly associated with a positive fatigue case definition or FAS score.

Conclusions

- Lower levels of physical activity at one month independently predicted greater FAS at six and 12 months post stroke. This study did not find evidence of an association between physical fitness measures and fatigue after stroke.

Chapter 6 - General Discussion and Conclusions

Summary of findings from thesis

This thesis aimed to investigate the frequency and natural history of fatigue after stroke and its associations with mood, physical activity and/or physical fitness.

Frequency and Natural History

The systematic review in Chapter Two and the longitudinal study in Chapter Four both found that fatigue is a common and persistent symptom after stroke. Clinically significant fatigue was still present in as many as a fifth of stroke survivors at 12 months after stroke onset. However the studies in both Chapter Two and Chapter Four also found that the frequency of fatigue decreases as time goes on, that most stroke survivors who have clinically significant fatigue at one month do not have clinically significant fatigue by six months after stroke onset and most individuals either report fatigue at all time points or report that they do not have fatigue at any time point.

Associations with mood, physical activity and/or physical fitness

Most of the studies identified in the systematic review in Chapter Three did not find a statistically significant relationship between fatigue and physical fitness but some studies reported an association between fatigue and physical activity. The longitudinal study in Chapter Five also did not find a statistically significant relationship between fatigue and measures of physical fitness such as hand grip strength, leg strength, leg power and six minute walk test score but did find there to be a significant association between physical activity as measured by daily step count and fatigue at each time point. Moreover, the longitudinal study found that daily step count at one month was an independent significant predictor of fatigue severity at six and 12 months. Interestingly, anxiety at one month was also found to be an independent significant predictor of fatigue severity at six and 12 months after stroke and was found to be a more important predictor of later fatigue than depression.

Evidence for the De-conditioning Model of fatigue after stroke

In the introduction chapter of this thesis it was postulated that fatigue after stroke may be caused by stroke survivors physically de-conditioning shortly after their stroke due to reducing their activity levels as a consequence of their neurological deficits.

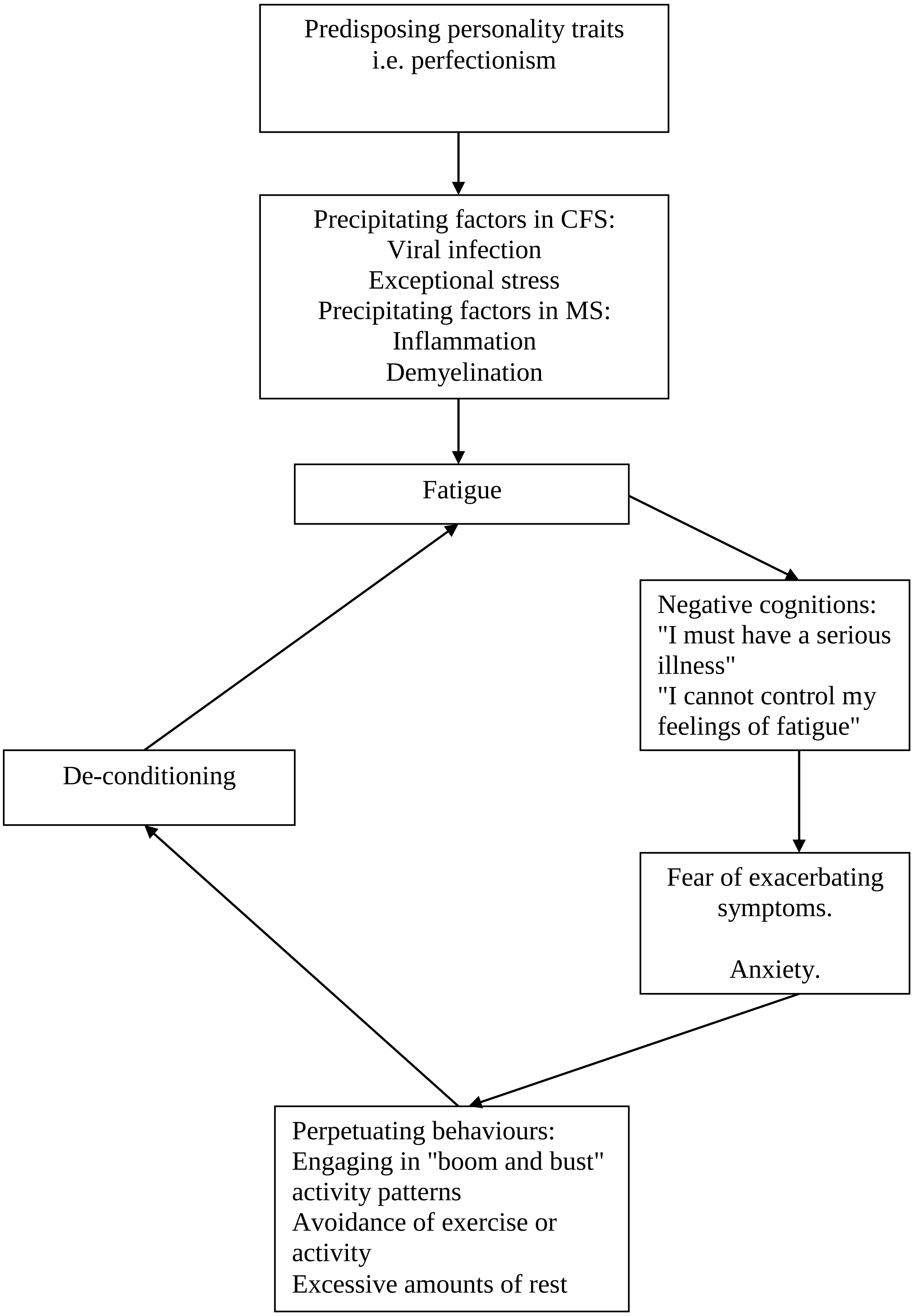
This thesis has only provided partial support for this de-conditioning model explanation of the cause of fatigue after stroke. In support of this model, this thesis found that the participants in the longitudinal study may have experienced some de-conditioning as their leg strength, leg power and hand grip scores were on average lower than have been found in an age-matched healthy population (Bohannon 2007; Skelton et al. 1994) and the longitudinal study in Chapter Five and one of the studies identified in the systematic review in Chapter Three found that lower daily step count was significantly related to higher levels of fatigue. However the de-conditioning model is not supported by the finding that most of the studies identified in the systematic review and the longitudinal study in Chapter Five did not find a statistically significant relationship between fatigue and measures of physical fitness which suggests that de-conditioning is not a cause of fatigue after stroke. In addition, the de-conditioning model does not explain the finding that higher levels of anxiety at one month predict higher levels of fatigue at six and 12 months after stroke. Therefore the de-conditioning model may be too simplistic and other factors may have to be considered when attempting to understand the causes of fatigue after stroke.

The Cognitive Behavioural Model of Chronic Fatigue Syndrome

One model of the aetiology of fatigue which has been suggested in the Chronic Fatigue Syndrome and the MS literature is the Cognitive Behavioural Model (Browne and Chalder 2009; van Kessel and Moss-Morris 2006; Vercoulen et al. 1998; Chalder, Butler and Wessely 1996).

The Cognitive-Behavioural Model (Figure 6.1) goes one step further than the de-conditioning model and is able to offer a potential explanation for why the fitness measures were not significantly associated with fatigue and why anxiety is an important predictor of later fatigue. This model suggests that de-conditioning by itself will not lead to fatigue in the long term. De-conditioning must be accompanied by the patient having a personality trait such as perfectionism which predisposes them to fatigue along with unhelpful beliefs or fears or negative interpretations of feelings of fatigue or symptoms of de-conditioning in order for fatigue to be perpetuated in the long term. For instance, some of the participants in the longitudinal study may have de-conditioned but if they did not focus on their bodily sensations or interpret bodily symptoms negatively then they may have remained active and therefore less likely to consider fatigue to be a problem for them. It is plausible that higher anxiety levels may influence how much a stroke survivor fears that activity is harmful to them or be concerned that their bodily symptoms are the sign of a serious illness and that is why higher anxiety at one month was found to be related to higher fatigue at a later time point in the longitudinal study.

Figure 6.1 - Cognitive-behavioural model of the aetiology of Chronic Fatigue Syndrome and fatigue in MS (Adapted from Browne and Chalder 2009, page 155 and van Kessel and Moss-Morris 2006, p 584)



Physical Activity and Fatigue

The de-conditioning model and the cognitive-behavioural model both suggest that low levels of activity can either cause or contribute to fatigue by leading to muscle de-conditioning. However an alternative viewpoint is that low levels of activity do not cause the problem but that high levels of physical activity can moderate and/or mediate the perpetuation of fatigue. In other words, even if low levels of activity are not causing fatigue, it is possible that high levels of activity may help to improve fatigue through mechanisms other than by preventing de-conditioning.

One possible mechanism by which activity may improve fatigue is that activity may reduce levels of factors which may perpetuate fatigue such as anxiety and/or depression in stroke survivors and this may in turn reduce fatigue severity. This potential explanation is plausible as several studies have reported exercise to have some moderate beneficial effects for depression (Eng and Reime 2014; Adamson, Ensari and Motl 2015; Cooney et al. 2013; Sjosten and Kivela 2006) and anxiety (Jayakody, Gunadasa and Hosker 2014; Wegner et al. 2014; Strohle 2009) and a systematic review did report that depression was significantly associated with fatigue after stroke and that anxiety had a tendency to be associated with fatigue after stroke (Wu et al. 2014). In addition, one of the longitudinal studies identified in the systematic review in Chapter Two of this thesis reported that depression and anxiety at two months post-stroke were independent predictors of fatigue at 18 months post-stroke indicating that anxiety and depression early after stroke could be a contributor to later fatigue (Snaphaan, van der Werf and Leeuw 2010). However in the longitudinal study in Chapter Five of this thesis, anxiety and physical activity were predictors of later fatigue severity which were statistically independent of each other. In other words anxiety was a predictor of fatigue severity at later time points even when activity levels are taken into account.

Another potential mechanism by which activity may improve fatigue is that increasing levels of physical activity may improve a stroke survivor's self-efficacy. Self-efficacy is defined as a person's belief in their own capability to be successful in a specific situation and is described as the most important factor in determining how much effort a person will invest in a particular task and how long they will persevere with that task when they encounter obstacles or difficulties. Self-efficacy has been reported to play a very important role in psychological adjustment and psychological problems (Bandura 1997; Bandura 1977). In stroke survivors, physical activity may increase their self-efficacy (and therefore their likelihood) to remain independent, return to work or their usual activities or to socialise. It is plausible that this may improve fatigue as it may increase stroke survivors' sense of control (Dimeo et al. 2008), and a more independent stroke survivor with a better social life may be less likely to focus their attention on fatigue symptoms or bodily sensations and if they are more likely to resume activities which matter to them they may perceive their fatigue to be less severe or less problematic which means they would be less likely to meet the criteria for clinically significant fatigue. Indeed, one recent study with stroke patients found there to be significant relationships between balance self-efficacy, chronic disease self-efficacy and fatigue (Miller et al. 2013). Another recent study reported that balance self-efficacy and participation in community walking were significantly associated (Robinson et al. 2011) suggesting a link between self-efficacy and exercise. Finally, one of the studies identified in the systematic review reported in Chapter Three did not find a direct association between fatigue and exercise but by using structural equation modelling techniques they found that there was an indirect relationship between fatigue and exercise "through self-efficacy expectations" (Shaughnessy, Resnick & Macko 2006, p17).

A third potential mechanism by which physical activity may improve fatigue is that physical activity may enhance neuroplasticity (Fuchs and Flugge 2014). Neuroplasticity refers to the brain's ability to reorganise, adapt or change itself over time. This involves neurons growing new nerve endings to reconnect to other neurons to form new neural pathways. These new neural pathways can result in a lost function or ability being regained. A recent systematic review of studies which tested the effects of exercise in animal models of ischaemic stroke reported that exercise can reduce the size of the brain lesion and improve neurobehavioural outcomes (Egan et al. 2014) suggesting that after stroke, physical activity can encourage the brain to recover. This may directly improve a stroke survivor's fatigue by repairing neurological processes or systems which may be involved with tiredness or indirectly improve their fatigue by improving factors which may contribute to fatigue such as functional ability or even depression. Indeed, a recent study (Kuppuswamy et al. 2015) has found evidence that fatigue may be a deficit in corticomotor excitability and there is some evidence in the literature that corticomotor excitability can be improved by exercise training (Fisher et al. 2008; Yen et al. 2008).

Anxiety and Fatigue

The cognitive-behavioural model also suggested that stroke survivors with higher anxiety levels are more likely to interpret feelings of fatigue or symptoms of de-conditioning very negatively, which will contribute to the perpetuation of fatigue. However there are several plausible alternative explanations regarding how anxiety may contribute to fatigue or why anxiety was found to be an independent predictor of fatigue in this thesis.

Firstly it is plausible that anxiety is associated with fatigue because increased anxiety causes increases in muscle tension. Studies have demonstrated that individuals who had higher anxiety levels used more objectively measured energy or exhibited more muscle fatigue than individuals with lower anxiety levels (Weinberg and Gould 2007) as tense muscles use up more energy and are more easily fatigued than relaxed muscles. Increased muscle tension can also have the effect of reducing an individual's co-ordination which could plausibly have the effect of reducing an individual's self-efficacy to do certain activities.

Another plausible reason why anxiety is associated with fatigue after stroke is that anxiety levels affect how much of the stress hormone cortisol is released by the body. The presence of abnormal levels of cortisol have been reported in the Chronic Fatigue Syndrome literature (Powell et al. 2013; Tomas, Newton and Watson 2013). However one study of stroke patients found no association between cortisol levels and fatigue (Radman et al. 2012).

Finally, several studies using animal models have reported evidence that stress actually reduces neuroplasticity (Fuchs and Flugge 2014) and this is another plausible explanation to why anxiety at one month post-stroke is associated with fatigue at six and 12 months post-stroke.

An association between anxiety and fatigue is not a new finding. Fatigue is listed as a known symptom of Generalised Anxiety Disorder (GAD) (Centres for Disease Control and Prevention, 2015) However, only a small number of the participants in the longitudinal study in Chapter Five had a HADS scores which would indicate that they had an anxiety disorder and there is no evidence that the fatigue reported by people with GAD is qualitatively the same as fatigue experienced after stroke.

Bio-psycho-social-behavioural model of fatigue after stroke

Although anxiety and physical activity were independent predictors of fatigue, the regression models in Chapter Five of this thesis found that these two variables, along with age, gender and fatigue before stroke, only actually accounted for approximately 22% and 27% of the variance in fatigue severity scores at six and 12 months respectively. This means that a model which includes more factors is required to explain the remaining variance in fatigue severity.

A recent review of the stroke literature suggested a bio-psycho-social-behavioural model for how fatigue may be precipitated and perpetuated in stroke patients (Wu et al. 2015). This model is presented in Figure 6.2. This model is similar to the cognitive-behavioural model in that it suggests that personality factors can predispose a person to fatigue, that fatigue is triggered by a precipitating factor (i.e. the stroke) and that reduced physical activity, anxiety and locus of control can influence the perpetuation of fatigue. However it differs from the cognitive-behavioural model in that it takes many more factors into account when describing how fatigue after stroke could be precipitated or perpetuated. These additional factors include brain lesions, inflammatory and neuroendocrine changes, residual neurological deficits, perceived disability, physical impairments, cognitive impairments, self-efficacy, passive coping, depression and social support. This model presents fatigue as a symptom which is complex and multi-factorial.

A prominent feature of this model is that a distinction is made between early and late fatigue after stroke. The model suggests that the presence of fatigue early after stroke directly contributes to the presence of fatigue at a later time point. Although the model does not specify a time frame between early and late fatigue, the results of the longitudinal study reported in Chapters Four and Five support the suggestion of a relationship between early and late fatigue as most participants in this study were either fatigued or not fatigued across all three time points and fatigue severity at one month was an independent significant predictor of fatigue severity at six and 12 months after stroke onset. The model also suggests that early fatigue may be influenced by different factors than late fatigue. For instance, early fatigue may be the result of the stroke itself in addition to psychological factors whereas late fatigue may be mostly the result of psychological factors. This model may help us understand the findings of this thesis that the frequency of clinically significant fatigue decreased and that fatigue severity improved over time. Many of the variables which this model suggests contribute to fatigue are modifiable. Stroke survivors' fatigue may have improved due to changes in one or more of these variables. For instance a stroke survivor may seek out treatment for depression or anxiety, increase their physical activity levels, learn better coping strategies or their significant others may become better at providing support.

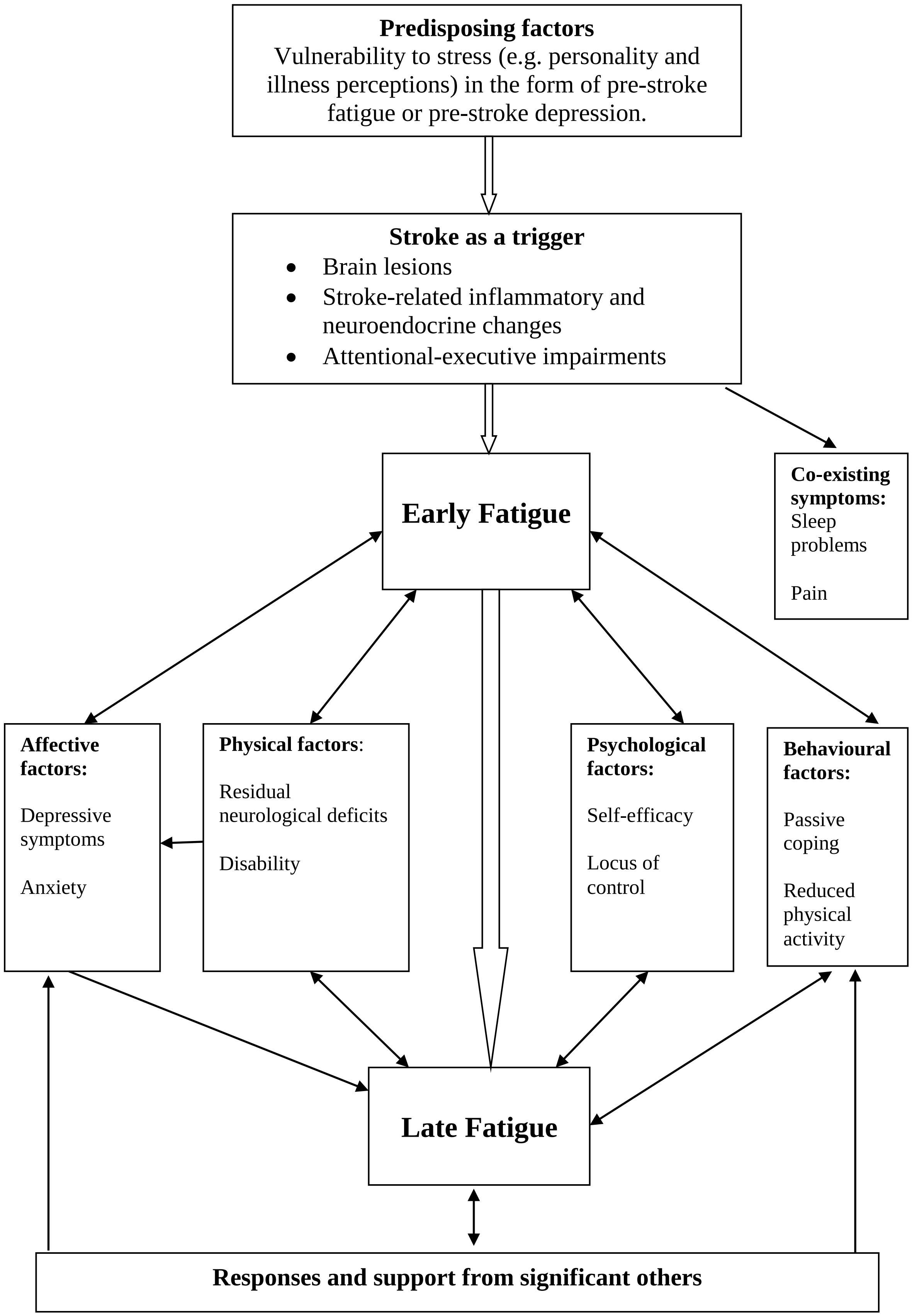
Alternatively some stroke survivors may be more affected by factors which contribute to early fatigue than by factors which contribute to later fatigue and this is why their fatigue status changes over time. For instance, a stroke survivor who is susceptible to biological causes of fatigue but resilient to psychological contributors to fatigue is likely to experience an improvement in fatigue over time whereas a stroke survivor who is not resilient to psychological factors is more likely to continue to have fatigue in the long term.

How the findings of this thesis relate to the Bio-Psycho-Social-Behavioural Model

The main findings of this thesis are consistent with this Bio-Psycho-Social-Behavioural model. Firstly, the regression models in Chapter 5 found that anxiety and physical activity at one month are independent predictors of fatigue at later time points. Both anxiety and physical activity were included as contributors to fatigue in the bio-psycho-social-behavioural model. The regression models in Chapter 5 with age, gender, fatigue before stroke, anxiety and physical activity only accounted for

22% and 27% of the variance in fatigue suggesting most of the variance in fatigue is explained by other factors. The bio-psycho-social-behavioural model suggests many other factors which could account for this variance. Chapter Four of this thesis reported that most participants were either fatigued or not fatigued at all three time points. This may support the suggestion in the bio-psycho-social-behavioural model that there is a relationship between early fatigue and late fatigue after stroke. Finally, Chapters Two and Four reported that the frequency of fatigue is more likely to decrease over time. The bio-psycho-social-behavioural model suggests many modifiable factors which contribute to fatigue and changes in these factors could account for this improvement in fatigue over time.

Figure 6.2 - A conceptual model of post-stroke fatigue (Wu et al. 2015, page 896)



Implications for Stroke Survivors and Clinicians

The results of this thesis have several practical implications for stroke survivors and clinicians who are involved in their management. For instance, the finding that fatigue is common very soon after stroke onset suggests that clinicians should assess patients for fatigue at follow-up visits as early as possible after stroke. The findings regarding the natural history of fatigue suggest that patients who report clinically significant fatigue shortly after stroke onset should be informed that although their feelings of fatigue are likely to persist in the long term it is likely that the severity of their fatigue will improve as time passes and they will perceive fatigue as less of a problem as time goes on. Patients who do not report clinically significant fatigue early after stroke should be reassured that although it is possible that they may develop a problematic fatigue at a later time point, it is more likely that they will not experience a problematic fatigue at least in the first 12 months after stroke onset. It is important that this information about the course of fatigue is disseminated to stroke survivors and their families by clinicians as lack of knowledge and information about fatigue after stroke and a lack of acknowledgement of the seriousness of fatigue from family members can lead to additional distress for the patient and make the fatigue more of a problem for them (Eilertsen, Ormstad and Kirkevold 2013; White et al. 2012; Ormstad et al. 2011).

The frequency and persistence of fatigue suggests that the development of an intervention for fatigue is warranted. However the optimum timing of the delivery of an intervention is debateable. It could be argued that the best time to deliver an intervention for fatigue would be straight after stroke onset to prevent it from developing in the first place or as soon as it first appears to prevent it from persisting in the long term. However at this time point stroke survivors are undergoing acute treatments and may perceive physical recovery to be more of a priority which may mean they are less motivated to engage with an intervention for fatigue. It should also be taken into account that by six months post stroke many stroke survivors will have recovered from clinically significant fatigue and their fatigue severity will have improved without the aid of an intervention. Therefore it may be best to deliver an intervention between six and 12 months post-stroke during this time period the rate of unaided recovery from fatigue has decreased which means that those who are still fatigued at this point may be more in need of help and therefore benefit the most from an intervention. If the model by Wu et al. (2015) is accurate and early fatigue is influenced by different factors than late fatigue then different interventions may have to be delivered at later time points than shortly after stroke onset.

Regarding the type of intervention which could be delivered, the results of this thesis suggest that an intervention which increases physical activity levels may be beneficial. Exactly what such a physical activity intervention would entail remains to be determined. There are many aspects of an exercise intervention that a clinician should consider and the stroke, MS, CFS and cancer literature does not provide the clinician with clear guidance on this matter. In the stroke literature there are no previous studies which have tested the effectiveness of a physical activity intervention on its own for fatigue. A study of stroke survivors by Zedlitz et al. (2012) compared one group of stroke survivors who received 12 weeks of cognitive therapy with those who received 12 weeks of a combination of cognitive therapy and graded activity training. Graded activity training involved walking on a treadmill and strength training which were slowly increased in amount and intensity from the beginning to the end of the study. Fatigue levels significantly reduced in both groups but the group that received the graded activity training showed greater improvement. However, it could be argued that the results of this study could have been confounded by the amount of intervention exposure that participants in each group had. In other words those participants who received GET and CBT may have showed more improvement simply because they were exposed to a double intervention rather than because of the content of the interventions. Across the MS, CFS and cancer literature interventions which involve aerobic exercise, resistance training, aerobic and resistance training combined, aquatic exercise and yoga have all been reported to be effective at reducing fatigue levels (Larun et al. 2015; Pilutti et al. 2013; Latimer-Cheung et al. 2013; Cramp and Byron-Daniel 2012). However due to the heterogeneity of all these studies it is still not known what the optimal frequency, duration and intensity of exercise is required to combat fatigue (Andreasen, Stenager and Dalgas 2011). In addition, it is also uncertain which types of exercise may be the most effective. In the MS literature interventions which include an element of resistance training are emerging as the most effective form of exercise training for reducing fatigue (Oral and Yaliman 2013; Latimer-Cheung et al. 2013; Andreasen, Stenager and Dalgas 2011) but a meta-analysis of cancer related fatigue studies reported that aerobic exercise significantly reduced fatigue but there was no statistically significant effect when resistance training and other forms of exercise were used as the intervention (Cramp and Byron-Daniel 2012). An additional consideration for the clinician is what is the best context in which to deliver an exercise intervention. One meta-analysis of exercise training in cancer patients reported that supervised exercise training resulted in a significant reduction in fatigue but unsupervised home or community based exercise programmes did not reduce fatigue by a statistically significant amount (McMillan and Newhouse 2011). The clinician must also decide how to deliver exercise interventions. In the Zedlitz (2012) study of stroke patients and many of the studies in the MS, CFS and cancer literature the patients' levels of activity were increased through supported Graded Exercise Therapy (GET) programmes. A GET programme involves a specialist working with the patient to gradually increase the amount and intensity of exercise that they do over time. Delivering an exercise programme gradually is very important as if the patient finds the exercise to be too strenuous they are unlikely to continue with the programme (Wyller 2007).

The results of this thesis also suggest that clinicians should ensure that all stroke patients are screened for anxiety and that patients with high anxiety levels are offered a suitable intervention as this may be of benefit to their fatigue levels. There are a number of treatments for anxiety that stroke survivors could consider. For instance, they could take certain medications, engage in a course of Cognitive Behavioural Therapy (Otte 2011) or those patients with less severe anxiety could use self-help books (Cuijpers and Schuurmans 2007; Haug et al. 2012), undertake a program of mindfulness meditation (Hoge et al. 2013; Lawrence et al. 2013), yoga (Kirkwood et al. 2005) or Tai Chi (Wang et al. 2014) to reduce their anxiety levels. Clinicians should also consider screening all stroke patients for depression and deliver an intervention to reduce depressive symptoms. This may also be beneficial as even though this thesis found that anxiety is a stronger predictor of fatigue than depression it did still find a significant bi-variate association between fatigue and depression at all three time points. Moreover, a meta-analysis of the psychosocial associations with fatigue in stroke patients reported there to be a statistically significant association with depression but only a "trend towards association" with anxiety (Wu et al. 2014, p4). There is some evidence in the MS and cancer literature that treating depression and/or anxiety can reduce fatigue levels (Induruwa, Constantinescu and Gran 2012; Barsevick, Newhall and Brown 2008; Krupp, Serafin and Christodoulou 2010; Johnson 2008).

Clinicians must take into consideration that physical activity and anxiety do not account for all the variance in fatigue severity at later time points and that other unknown variables are probably also contributing to fatigue severity. Therefore an intervention which only targets low activity levels and/or high anxiety still may not be sufficient in treating fatigue after stroke. The stroke literature has reported many biological, psychosocial and behavioural factors to be associated with fatigue (Wu et al. 2014) and it is likely that each individual will have a different combination of issues which influence their fatigue. This suggests that clinicians may have to take a multi-disciplinary approach to fatigue management which takes into account each individual's specific problems and desires. This concept of multi-disciplinary, individualised approach to fatigue management has often been suggested in the MS and cancer literature (Induruwa, Constantinescu and Gran 2012; Berger, Gerber and

Mayer 2012; Bruera and Yennurajalingam 2010; Fernandez et al. 2009; Griffiths and Zarrouf 2008).

Suggestions for future research

Firstly, it is important that researchers reach a consensus regarding how to assess post-stroke fatigue in future so that studies can be directly compared. The literature review in Chapter One and the systematic review of longitudinal studies in Chapter Two demonstrated the diversity of methods for assessing fatigue. Although some were quite similar, others were very different and comparisons may not be very meaningful. Similarly, pre-stroke fatigue should be assessed with the fatigue case definition or at the very least the same method as post-stroke fatigue is assessed. It should be taken into account that pre-stroke and post-stroke fatigue may be so different from each other that even if the same instrument was used, meaningful comparisons would still not be possible.

It is important that larger longitudinal studies are carried out in the future. The longitudinal study in Chapter Five found no significant association between fatigue and measures of fitness. However, it is possible that a significant relationship between fitness and fatigue was not found due to there being a lack of statistical power which means it still remains highly plausible that de-conditioning may contribute to fatigue. Therefore a larger study investigating associations between fatigue and fitness should be carried out. A study which investigates whether de-conditioning is associated with fatigue only in more anxious individuals would be interesting as this would be consistent with the cognitive-behavioural model which states that a combination of de-conditioning and negative interpretation of the symptoms perpetuates fatigue. Likewise, it would also be interesting to investigate whether certain personality traits such as perfectionism are associated with fatigue in stroke survivors as has been reported in the CFS literature.

Future larger longitudinal studies should assess the relationships between a number of variables and fatigue. Many variables have been reported to be associated with fatigue or contributing to fatigue as depicted in the model by Wu et al. (2015) but it still needs to be investigated how much of the variance in fatigue each factor contributes and the direction of causality between different variables and fatigue and whether variables are directly or indirectly related to each other. A limitation of the longitudinal study in this thesis is that it cannot definitively prove that low activity and high anxiety actually cause high fatigue, it is still plausible that fatigue may cause low activity and high anxiety or there may be other unknown variables involved. Analysing large longitudinal studies by using Structural Equation Modelling (SEM) techniques could potentially provide evidence regarding the direction of relationships between several factors and fatigue and how much variance each factor contributes. These modelling techniques could also potentially provide evidence for the suggestion that different factors may contribute to fatigue which occurs early after stroke onset than fatigue which occurs later. Indeed, the longitudinal study in Chapter Five identified that a small number of participants did not have clinically significant fatigue at the one month time point but then went on to develop it at either the six or 12 month time points. Using modelling techniques to compare these people with those who did not develop fatigue at all or with those who developed it straight away may be useful as it could suggest which factors are associated with the development of fatigue over time. It was not possible to use SEM techniques when analysing the data collected in this thesis as they generally require more cases than were available. It is very important to do this type of analysis as it could potentially lead to a better understanding of the factors that contribute to fatigue and this could enable better treatments to be developed.

The details of an example future longitudinal study are presented in Table 6.1. This example longitudinal study includes most of the factors which were suggested in the Wu et al. (2015) model.

Table 6.1 - Characteristics of a potential longitudinal study of fatigue after stroke.

Eligibility Criteria	Inclusion criteria: • Diagnosis of first ever strokes (ischaemic or haemorrhagic). • Cognitively able to complete questionnaires with or without help. Exclusion criteria: • Diagnosis of T.I.A. without stroke diagnosis. • Presence of other neurological conditions such as Parkinson's Disease and Multiple Sclerosis. • Presence of other conditions which are associated with chronic fatigue such as cancer or Traumatic Brain Injury. • Anyone previously diagnosed with Chronic Fatigue Syndrome.
Assessment time points	Baseline, 1 month, six months, 12 months and 24 months after stroke onset.
Variables (measures)	Dependent variable: • Fatigue (MFI-20 fatigue questionnaire) Independent variables: • Anxiety (HADS) • Depression (HADS) • Self-efficacy (The Chronic Disease Self-efficacy Scale (CDSE) (Miller et al. 2013) and the Short Self-efficacy

	for Exercise Scale (SSEE)) (Shaughessy, Resnick and Macko 2006). • Personality traits (NEO Personality Inventory and The Multi-dimensional Perfectionism Scale) (Deary and Chalder 2010). • Social support (The ENRICHD Social Support Inventory (ESSI)) (Gottlieb and Bergen 2010). • Coping skills (Coping Inventory for Stressful Situations) (Jaracz, Mielcarek and Kozubski 2007) • Locus of control (The Multi-dimensional Health Locus of Control Scale) (Wallston and Wallston 1978). • Disability (Modified Rankin Scale) • Residual neurological deficits (NIHSS) • Physical activity (Either use the ActivPaL™ again or use a heart rate and movement combination (HR+M) monitor (Strath et al. 2002)). • Physical fitness (same measures as those described in Chapter 5 but use portable equipment that can be taken to participant's homes)
Analysis (number of participants required)	Three separate statistical analyses: • Structural Equation Modelling (Sample sizes needed for a reliable SEM model is a topic of debate. Several factors such as the amount of missing data or how normally distributed the data are have an effect on how many cases are required (Wolf et al. 2013). Ideally should carry out own Monte-Carlo simulation study to determine the required sample size (Muthen and Muthen 2002)). • Multiple linear regression models at each time point which include the Psycho-social-behavioural variables (at least 10 participants per variable included in the model). • Two-way ANOVA at each time point to determine if there is an interaction effect on fatigue between different levels of anxiety and physical fitness. (120 participants required)

However these modelling techniques still do not prove causality. The only way to prove whether a particular factor actually causes fatigue would be to carry out a randomised controlled trial (RCT). Therefore one suggestion for future research would be to carry out large RCTs to test interventions which increase activity and /or interventions which reduce anxiety with fatigue as an outcome measure. The details of such an RCT are presented in Table 6.2. This example RCT includes a group which receives an intervention for anxiety, a group which receives an intervention to increase daily step count, a control group (participants attend a general stroke education class) and a fourth treatment group where participants receive an intervention for anxiety in combination with one to increase physical activity. This fourth treatment group is a factorial design which makes it possible to investigate whether there are interactions between the effects of the two treatments. In other words it will test whether an activity intervention will only work if the stroke survivor's anxiety levels are being managed at the same time. (Although a potential criticism of adding this fourth treatment group is that the participants in this group could potentially show an improvement simply because their intervention exposure was double that of participants in the other groups rather than because of the content or nature of the intervention. However having this group in the study design could still provide useful and interesting information about any interactions between the two variables and therefore should still be included). This example RCT would be a starting point for investigating activity based interventions in the treatment of fatigue after stroke. Further RCTs could involve different types, frequencies, intensities and durations of activity to find the optimum treatment of fatigue and they could also investigate whether lifestyle activity such as walking in the community or structured instituition based activity such as supervised treadmill walking would be more effective.

In the MS, CFS and cancer literature, in addition to exercise, another treatment for fatigue which has been consistently reported to be effective is Cognitive-

Behavioural-Therapy (CBT) (Larun et al. 2015; Bower 2014; White et al. 2013; Induruwa, Constantinescu and Gran 2012; Kos et al. 2008; Barsevick, Newhall and Brown 2008; Stone and Minton 2008; Wyller 2007; Devanur and Kerr 2006). In theory CBT treats fatigue as it challenges negative cognitions or fears that patients may have about their symptoms and encourages patients to change certain behaviours such as avoidance of activity in order to prevent the long term perpetuation of fatigue (White et al. 2011). Therefore future RCTs should investigate whether specifically CBT may be effective at treating fatigue in the stroke population.

Wu et al. (2015) suggested that fatigue which occurs early after stroke may be different from fatigue which is present later after stroke onset. Therefore it might be interesting for a further RCT to compare interventions that were delivered early after stroke with interventions delivered later after stroke. (Potentially this could be investigated by carrying out a sub-group analysis of any data collected for the RCT described in Table 6.2).

Finally, this thesis has shown that the frequency and severity of fatigue decreases over time therefore RCTs which aim to evaluate interventions for post-stroke fatigue must use a control group to determine whether any reduction in fatigue is due to the intervention rather than because of the natural history of fatigue, particularly if an intervention is delivered between one and six months. It is also important to consider only including fatigued patients in any future RCTs in order to prevent a "floor effect" (Motl and Pilutti 2012, p495).

Table 6.2 – Characteristics of a potential RCT of treatments for fatigue after stroke.

Eligibility Criteria	Inclusion criteria: • Diagnosis of first ever strokes (ischaemic or haemorrhagic). • Cognitively able to complete questionnaires with or without help. • Fulfils fatigue case definition criteria Exclusion criteria: • Diagnosis of T.I.A. without stroke diagnosis. • Presence of other neurological conditions such as Parkinson's Disease and Multiple Sclerosis. • Presence of other conditions which are associated with chronic fatigue such as cancer or Traumatic Brain Injury. • Anyone previously diagnosed with Chronic Fatigue Syndrome.
Stratification	• Time since stroke (< 6 months or between 6 and 12 months) • Mood disorder at time of enrollment to study • Fatigue before stroke (as assessed by fatigue case definition)
Interventions	Intervention programmes would last 12 weeks • Control group - attendance at a general stroke education class • Intervention to increase daily step count (GET) • Intervention to reduce anxiety • Intervention to increase daily step count and reduce anxiety (GET plus anxiety treatment).
Outcome measures	Taken at baseline, 6 weeks, 12 weeks and 24 weeks. Primary outcome measures: • Percentage of participants who fulfil fatigue case definition. • MFI-20 score Secondary outcome measures: • Mood • Quality of life
Numbers needed	150 participants per treatment group

Conclusion

This thesis has made more than one original contribution to the research on fatigue after stroke. It sought to understand the frequency and natural history of clinically significant fatigue over the first year after stroke onset and found it to be a common and persistent symptom. This thesis also sought to explore whether lack of physical activity after stroke or whether the patient's mood were associated with fatigue and found that these factors to be significant contributors to fatigue but that there were likely to be several other factors which influence a stroke survivor's experience of fatigue.

Therefore considering the high frequency of fatigue, the length of time it persists for and the detrimental impact that fatigue can have on a stroke survivor's life it is vital that more research is carried out on potential interventions for established fatigue and ways in which it might be prevented.

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Appendix 1- Published paper "Frequency and natural history of fatigue after stroke: A systematic review of longitudinal studies"

The full reference for this paper is: Duncan F., Wu S. and Mead G.E. (2012) Frequency and natural history of fatigue after stroke: a systematic review of longitudinal studies. *Journal of Psychosomatic Research*. 73(1), pp 18-27.

Abstract

Background: Fatigue is a common and distressing symptom after stroke. Stroke survivors and health professionals need to know whether fatigue is likely to improve, or get worse over time; and whether there is a temporal association with depression or anxiety, which might provide a target for treatment,

Aims and objectives: to systematically review all longitudinal observational studies which have assessed fatigue on at least two separate time points after stroke onset to determine its frequency, natural history and temporal relationship with anxiety and/or depression.

Method: We systematically searched MEDLINE, EMBASE, CINAHL and PsycInfo using the keywords “fatigue” and “stroke” and their associated terms or synonyms. Data were extracted regarding time points after stroke where fatigue was assessed, frequency of fatigue at each time point and any reported associations with anxiety and/or depression.

Results: 101 full texts were retrieved after scrutinising the titles and abstracts. Nine fulfilled our inclusion criteria. Fatigue was assessed at a variety of time points after stroke (from admission – to 36 months). The frequency of fatigue ranged from 35%-92% at the first time point. Frequency of fatigue declined across time points in seven of the studies (n = 764) and increased in two studies (n = 195). Three papers found significant associations between fatigue and mood at the same time point. The single study investigating temporal associations between fatigue and mood disorders reported that depression predicted subsequent fatigue.

Conclusions: Fatigue is present soon after stroke onset and remains common in the longer term. There is little evidence regarding the temporal relationship between fatigue and mood: this is an area where further research is needed.

Introduction

Fatigue can be defined as a chronic subjective “feeling of lack of energy, weariness and aversion to effort” [1]. After stroke, fatigue is common and distressing to patients, for example, a recent study reported that 43% of stroke survivors felt they were not receiving enough help for fatigue. [5]. Fatigue is an independent predictor of institutionalization [2, 3] and, for stroke survivors under the age of 60 years, an independent predictor of being unable to return to paid work [4].

It is crucial to understand the natural history of fatigue after stroke. Stroke survivors need to know whether their fatigue is likely to improve over time, stay the same or progressively get worse so they can plan their future e.g. returning to work or resumption of previous leisure activities. Health care professionals need to know how many stroke survivors are likely to be fatigued at different time points so services can be planned accordingly. Researchers need to know whether fatigue starts immediately after stroke and how long it lasts, in order to decide how soon after stroke an intervention for fatigue should be delivered (if one could be developed).

Longitudinal studies have major advantages over cross sectional studies when studying the natural history of a condition or symptom because they report changes within individuals as well as the proportion of patients at a particular time point who have a symptom. Therefore longitudinal studies of post-stroke fatigue could tell us if fatigue is a stable symptom or whether it fluctuates over time. Longitudinal studies can also provide information about whether fatigue affects all patients for a short period of time or a small number of patients over an extended period; cross-sectional studies are unable to provide this information [40].

Several cross-sectional papers have demonstrated an association between fatigue and depression after stroke. [6, 7, 8, 9] leading to the suggestion that fatigue is a symptom of post-stroke depression

[10,11]. However, identifying an association between these two symptoms at a particular time point does not necessarily mean that one symptom causes the other, or vice versa; it is equally plausible that a third factor might cause both symptoms [36]. Longitudinal studies can potentially provide evidence regarding the direction of any observed association between fatigue and mood disorders i.e. whether depression precedes fatigue or vice versa. [37] Understanding the direction of causality is important because if depression precedes fatigue then identifying and treating depression might prevent or reduce the risk of developing post-stroke fatigue.

There are several published non systematic narrative reviews of fatigue after stroke [1, 12, 13, 14, 15, 16]. *Systematic* reviews are scientifically more robust and are consequently considered to be more objective sources of information and less prone to bias and error than traditional narrative reviews [18, 19]. The single previous systematic review used narrow search terms and so may have missed studies. Furthermore, the searches were performed in 2009, and we know of other studies on post-stroke fatigue that have been published since then [17]

The aim of this systematic review was to identify all longitudinal observational studies of fatigue after stroke to determine the frequency of fatigue, its natural history and the temporal relationship between fatigue and mood disorders.

Method

Searches

Searches were conducted in MEDLINE (from 1966), EMBASE (from 1980), CINAHL (from 1937) and PsycInfo (from 1806) on 7th April 2011 using keywords "fatigue" and "stroke" and their associated terms or synonyms. The same search terms were used in this review as in the published Cochrane systematic review [20] of interventions for post-stroke fatigue (Appendix 1).

Definition of stroke

Stroke was defined as "a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and those with subarachnoid haemorrhage), loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" [42].

Study selection

One reviewer (FD) removed all duplicates using Endnote, and then scrutinised unique titles and their abstracts. Those abstracts that were potentially relevant were obtained as full texts. Reference lists of the retrieved articles where fatigue after stroke was the dominant topic (including reviews, qualitative, cross sectional and longitudinal studies) were scrutinised for further potentially relevant studies. One reviewer (FD) applied the following inclusion criteria to all articles that had been retrieved as full texts; any uncertainties were resolved by discussion with a second reviewer (GM). Our inclusion criteria were:

1) written in English

2) published as a full text article in a peer review journal

3) recruited people with stroke (first or recurrent, ischaemic or haemorrhagic) > 18 years old

4) retained 10 or more participants for the duration of the study

5) specifically assessed and separately reported the presence or absence or fatigue using a single question, a case definition or a specified cut-off on a fatigue scale; or reported fatigue scores as a continuous variable

6) assessed fatigue on at least two separate occasions at least one month apart

7) recruited participants prospectively

8) the first measurement of fatigue was not more than 6 months after stroke onset.

Publications were excluded if:

1) they were only published in abstract form

2) they contained no primary data (e.g. reviews, editorials)

3) it was not possible to separately extract data for stroke patients from other types of patient

4) they recruited participants retrospectively

5) they used only an unstructured assessment of fatigue (e.g. qualitative assessments of fatigue where the specific questions asked may have varied from patient to patient)

6) assessed fatigue of patient only by asking carers or relativ

Data extraction

Two reviewers (FD and SW) independently extracted data (onto paper data collection forms) describing a) age, gender, sample size, time since stroke for each follow up, type of stroke. b) methods of measuring fatigue and/or mood, total number of participants who completed fatigue part of study at each time point. c) number of times fatigue was separately assessed and time between each assessment d) any reported frequencies of fatigue, depression and/or anxiety. e) any reported associations between fatigue and anxiety or depression.

Data Synthesis

The intention was to perform a meta-analysis in order to ascertain an estimate of the frequency of fatigue at different time points after stroke. However this could not be done due to the heterogeneity between the included studies regarding the time points that fatigue was assessed at, methods of assessing fatigue and populations from which participants were recruited. Instead, details of included studies were tabulated and a narrative data synthesis approach was undertaken.

Methodological Quality assessment

There is no clear consensus amongst researchers regarding which tool to use when assessing the quality of observational studies included in systematic reviews [21]. The Downs and Black checklist was chosen as the tool for assessing the quality of the studies included in this review as it was developed for use in observational studies as well as randomised trials [22]. It provides an overall score for study quality and a profile of scores for quality on four separate subscales; quality of reporting, internal validity, power and external validity. Fourteen of the 27 items are applicable to observational studies which do not provide an intervention. All 14 items were applied by one reviewer (FD) and a score of 0 or 1 given for each item.

Results

The electronic search identified 7046 citations before duplicates were removed. The full texts of 101 potentially relevant papers were retrieved. A further seven papers were retrieved following scrutiny of the reference lists of papers (reviews, qualitative, cross-sectional and longitudinal studies) where the main topic was fatigue after stroke. (Figure 1).

Of these 108 papers, 99 were excluded. The main reasons for excluding a study were a) it was a review and contained no original research b) it was cross sectional and fatigue was only assessed at one time point c) it recruited fatigued patients retrospectively d) it mentioned post-stroke fatigue but did not specifically report fatigue data for participants.

Our searches identified three studies that nearly met our inclusion criteria. One study [32] had to be excluded as 12% of the participants had had transient ischaemic attack, rather than stroke and the study did not separately report the data for the stroke patients. Another study was excluded as it reported energy subscale mean scores instead of frequency of fatigue at each time point [33]. A third study performed a number of psychosocial measurements on subarachnoid haemorrhage survivors at 3, 9 and 18 months after stroke onset but reported the frequency of fatigue only at the 9 and 18 month time points [34, 35]. Thus, nine studies, recruiting a total of 959 participants fulfilled our inclusion criteria (table 1).

Demographic characteristics

Five studies (n = 647) included patients with ischemic and haemorrhagic strokes [23, 24, 25, 28, 30], one (n = 108) included patients only with ischemic strokes [27] and three (n = 204) only included patients with subarachnoid haemorrhage [26, 29, 31]. Six studies (n = 463) recruited participants from hospitals [25, 26, 27, 28, 29, 31], two (n = 390) from rehabilitation centres [23, 24], and one (n = 106) recruited from a several sources [30]. Seven studies (n=823) only included first ever strokes [23, 24, 25, 26, 28, 29, 30], one (n = 108) included first or recurrent strokes [27] and one (n = 28) did not specify which types of stroke were included [31]. The mean age of the participants ranged from 45.5 years [29] to 73.3 years [30]. The proportion of males ranged from 33.7% [29] to 64% [27].

Assessment of fatigue

A variety of instruments were used to assess fatigue: two studies used the Fatigue Severity Scale (FSS) [23, 24], one used the Multidimensional Fatigue Inventory (MFI-20) [25], one used the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) [26], one used the Checklist Individual Strength Fatigue Subscale [27] and the remaining four studies either used either a single question [28, 29] or a single item from a longer instrument [30, 31].

Methods used for assessing fatigue

Multi-item scales

Five papers used multi-item scales for assessing fatigue. There are slight differences regarding exactly what each multi-item scale measures. The FSS concentrates on how fatigue impacts on the daily life of a stroke survivor. The items on the CIS and the general fatigue subscale of the MFI-20 are very similar and assess symptoms that could be categorised as physical fatigue. The fourth multi-item scale, the MFSI-SF is more diverse. It consists of five subscales; general fatigue, emotional fatigue, mental fatigue, physical fatigue and vigor from which an overall score is calculated.

The two studies that used the FSS used very similar cut-off scores for fatigue. On the FSS, participants respond on a 7 point scale to nine statements and their score is the mean of all nine items. One study had a cut-off score of above 4 [23] and the other used a cut-off score of equal to or more than 4 [24]. The other three scales all use a different scoring system so it is not possible to directly compare the cut-off scores of these multi-item scales to each other. However it is possible to compare the labels that each study attributed to patients who scored above their respective cut-off score and these labels did differ quite significantly. One study labelled those above their specified cut-off as "having a moderate to high impact of fatigue" [23], another labelled patients as "fatigued" [24], one study reported that scoring above the cut-off point was "indicative of severe fatigue" [27], another that it was "indicative of an abnormal or pathological fatigue" [26], the final study labelled those scoring above the cut-off score as "suffering from a clinically significant pathological fatigue" [25].

In both the studies that used the FSS, the mean score at 12 months was 4.7 indicating that fatigue severity is similar across both these samples [23, 24].

Single question or single item assessments

Four papers used a single item or a single question to assess fatigue [28, 29, 30, 31] Each question or item in these studies was slightly different. Two of the included studies presented stroke survivors with a list of symptoms which included fatigue. In one study participants were asked to indicate which symptoms they had "experienced" recently [31]. In the second study participants were asked to indicate which symptoms they had been "troubled by" recently [30]. In the third study participants were asked if they were frequently more fatigued than before their stroke and they answered either yes or no [29]. The fourth study used the Neurobehavioural Rating Scale which involves a clinician interviewing each participant for 15-20 minutes. One item on the scale concerns fatiguability. The clinician observes the participant during the interview and makes a judgement regarding the participant's fatiguability during tasks or whether they appeared lethargic [28].

Timing of fatigue assessments

Five studies (n = 403) assessed fatigue at two time points [26, 27, 28, 29, 30], three (n = 418) at three time points [23, 24, 31] and one (n = 138) assessed fatigue four separate time points [25]. A variety of time points were used to assess fatigue. First assessments of fatigue were carried out at admission in one study (n = 167) [23], 10 days (n = 138) [25], one month (n = 13) [28], 10 weeks (n = 89) [29], 2 months (n = 108) [27], 3 months (n = 106) [30], 6 months (n = 251) [24, 31] and mean of 109 days (n = 79) after stroke [26]. Two assessed fatigue at 3 months (n = 244) [25, 30], four at six months (n = 431) [23, 24, 28, 31], six at 12 months (n = 713) [23, 24, 25, 29, 30, 31], one at 18 months (n = 108) [27] and two at 24 months (n = 157) [25, 31]. No two studies assessed fatigue at the same combination of time points.

Time course of fatigue

Seven of the studies (total n = 764) reported that the proportion of patients with fatigue decreased over time [24, 25, 26, 27, 28, 29, 30]. Only two studies (n = 195) reported that it increased over time [23, 31].

Four studies reported whether there was a statistically significant difference in fatigue scale scores between time points. One study (n= 167) reported that fatigue scores were significantly higher as time went on [23], whereas two studies (n = 244) found fatigue scores to be significantly higher at the first time point [25, 30] and the other study (n=87) found no significant differences in fatigue scores across the time points [26].

Course of fatigue after stroke for individual patients

Three studies investigated whether it was the same participants who were fatigued or not fatigued across all time points or whether a more complex course of fatigue exists for each individual [23, 25, 27]. One of these studies (n = 167) reported that fatigue was present at all three time points in 37.7% of participants and was absent at all three time points in 17.4% of participants [23]. Another study (n = 108) found that 57% of patients did not have fatigue at any time point and 26% had fatigue at both time points. This study also reported that 9% had recovered from their fatigue between two and 18 months post stroke and 8% had developed fatigue between two and 18 months post stroke [27]. The third study (n = 138) reported that fatigue was a stable symptom with 72% of their participants remaining either fatigued or non-fatigued between 10 days and three months and 75% between three months and two years. This study also reported that only 9% of participants developed fatigue between three months and two years [25]

Relationship between fatigue and mood

The second aim of this systematic review was to explore the temporal relationship between fatigue and mood. Eight of the included studies assessed depression and/or anxiety. Four of these studies [28, 29, 30, 31] reported the frequency of depression at each time point but did not report any associations between depression and fatigue. One study did not report the associations between fatigue and mood but commented that depression may be a confounder of the relationship between fatigue and health related quality of life [24]. The remaining three studies (n = 167, 138, 87) reported data on the relationship between fatigue and mood [23, 26, 27] (table 2).

All three of the studies reported that depression and/ or anxiety were significantly associated with fatigue, when fatigue and mood were assessed at the same time point [23, 26, 27]. Only one study reported the temporal relationship between mood and fatigue [27]. This study reported that higher depression and / or anxiety scores at two months after stroke onset predicted higher fatigue scores at 18 months after stroke onset. This study also found that participants who were depressed at two months, but not fatigued, went on to develop fatigue by the 18 month follow up. This suggests that, in this cohort depression preceded fatigue.

Methodological Quality

The total scores on the Downs and Black quality assessment checklist ranged from 9-13 with a median score of 11 out of a maximum score of 14. The checklist identified weaknesses in each of the three subscales of Reporting, External Validity and Internal Validity (Table 3). Six studies [23, 24, 25, 27, 29, 31] did not describe the characteristics of participants that had been lost to follow up and four of these studies [23, 25, 27, 29] did not take into account these losses when performing their statistical analyses. Six studies [23, 24, 26, 27, 28, 31] did not report the proportion of eligible patients who agreed to take part. This means that it is difficult to determine whether their sample is representative of the entire population from which they were recruited.

Discussion

This systematic review of longitudinal studies of post-stroke fatigue has demonstrated that the frequency of fatigue varied substantially between studies, with estimates ranging from 35% - 92% at first time point, probably reflecting the heterogeneity between the studies regarding the methods of recruitment and their methods of assessing fatigue.

Fatigue appears to be a persistent symptom after stroke at least for the first 36 months. The proportion of patients with fatigue at the beginning and end of each study was similar and the fatigue levels of individuals mostly remained stable over time.

The natural history of post-stroke fatigue has, to date, not been a salient topic in the literature. Consequently the reasons why fatigue persists for such a long time after stroke remain unknown. The symptom is likely to have both biological [41] and psychosocial [8, 10, 14, 16, 17] causes and in order to understand why fatigue is so persistent it is necessary to understand how these different factors inter-relate to each other over time.

We sought evidence of a temporal relationship between mood and fatigue. Only one study reported this relationship and demonstrated that those that developed fatigue over time were more depressed at baseline that those who did not develop fatigue at long term follow up suggesting that in some individuals depression predicts subsequent fatigue [27]. Temporal associations between fatigue and depression have been reported in several studies on fatigue in cancer and Multiple Sclerosis [38, 39]. However this research has not been able to reach a consensus on whether depression causes fatigue, fatigue causes depression, the relationship is bi-directional or whether a third unknown factor is responsible for both.

Mood is only one potential mechanism that may influence the course of post-stroke fatigue over time. The literature has reported pain [2, 51], sleep disorders [7, 9, 2, 43], disability levels [43, 44, 45], neurological impairment [45] and locus of control [23] to be associated with post-stroke fatigue. All these factors can change over time for individual stroke survivors and thus either perpetuate or mitigate fatigue.

In addition, these factors might in theory contribute to the characteristics of post-stroke fatigue that a patient suffers from. Some authors have observed [48, 49, 50] that fatigue may manifest itself in different ways. For instance some stroke patients may describe their feeling of fatigue as being mainly physical while others may experience a more mental fatigue. The type of fatigue being assessed did differ between some of the included studies. One of the included studies specified that it was mental fatigue that was being assessed [28]. The studies that used the CIS and the MFI-20) assessed physical fatigue [25, 27]. The study that used the MFSI-SF assessed mental, emotional, physical, general fatigue and vigour but reported the percentage of patients who scored above the cut-off after the total score was calculated meaning that it was not possible to extract data on the frequency of patients with each type of fatigue [26]. It is unlikely that these forms of fatigue are completely distinct from each other as each type may influence the presence or absence of another type. Future research could attempt to identify whether certain types of fatigue are more common in some patients than others in order to determine if individually tailored treatments for post-stroke fatigue are needed.

The results of this systematic review are similar to previous reviews in that they also reported PSF to be a common complaint and that its frequency varied between studies [1, 12, 13, 14, 15, 16, 17]. These previous reviews also reported that fatigue is associated with mood. In two of the reviews [14, 15], the only longitudinal paper that was discussed was the study that reported fatigue prevalence to increase over time [23], whereas our review showed that fatigue prevalence decreased over time in seven out of the nine included studies. The only other systematic review of PSF [17] identified just three longitudinal studies [23, 24, 25]. None of the previous reviews contained a discussion on the potential temporal association between fatigue and mood.

Previous reviews did not specify whether they included or excluded subarachnoid haemorrhage (SAH) patients in their definition of stroke. For this systematic review we chose to include studies that assessed fatigue in SAH patients. It could be argued that these patients should not have been included because they are not directly comparable to intracerebral haemorrhage and ischaemic stroke patients because SAH has a different aetiology, risk factor management and affects a younger age group. However the aetiology and mechanisms of post-stroke fatigue are not yet understood and SAH patients still have many factors in common with other stroke patients such as sudden onset of disease, long term disabilities and the psychological distress of the event. In addition to this, it would not have been possible to exclude fatigue data for all SAH patients included in our review as three studies [23, 25, 28] did not specify whether SAH was included or excluded from their sample and one study [24] reported that they did include SAH patients but it was not possible to separate fatigue data for these patients from other stroke patients in their sample.

Strengths of this systematic review

This review focused on two questions that are of critical importance to stroke survivors. It used a rigorously developed protocol with clearly pre-specified inclusion and exclusion criteria which were agreed in advance of performing the searches. Numerous synonyms of the words "fatigue" and "stroke" were used in the search. Furthermore two authors independently extracted data.

Limitations of this review

Although we used a wide range of synonyms for fatigue in our search strategy (e.g. asthenia, lethargy, weariness, exhaustion, lassitude, listlessness, malaise), we did not include words such as energy or vitality unless they were preceded by the words "low" or "lack of". Thus studies which assessed fatigue using an energy subscale of a quality of life instrument e.g. the vitality scale of the SF-36 may have been missed. However this is unlikely as we carefully scrutinised reference lists of key papers to help ensure that we did not miss studies that fulfilled our inclusion criteria.

We pre-specified that only studies published in the English language would be included. In theory relevant studies published in other languages may have been missed. However all foreign language papers identified by the search had English abstracts and based on scrutinisation of the English abstracts, none of them would have fulfilled our inclusion criteria.

Another limitation of this review is that study selection was carried out by the only one author (FD), but a second author was available to discuss any uncertainties about whether to include or exclude studies. The assessment of the quality of the studies was also performed by one researcher but we believe it is highly unlikely that the results of the review would have changed substantially should a second author had also assessed quality.

Limitations of studies in review

The Black and Downs quality assessment tool [22] demonstrated limitations of the studies included in the review. Six studies [23, 24, 25, 27, 29, 31] did not describe the characteristics of the participants who were lost to follow up. It is possible that patients with more severe fatigue may have been more likely to have dropped out and this may have led to an underestimation of fatigue frequency at later time points. On the other hand those who were fatigued at the first time point may have been *less* likely to drop out as they may have wished to continue to participate in research and this would have led to the frequency of fatigue being overestimated at later time points. Six studies [23, 24, 26, 27, 28, 31] did not report the proportion of eligible patients agreeing to take part, and so the sample may not be representative of all strokes.

In addition, two of the studies included small samples sizes (n= 13, 28) which means they provide a lower precision estimate of the frequency of fatigue, four studies [28, 29, 30, 31] used a single question to assess fatigue which may not be an adequate method of measuring a multidimensional construct, and two studies [23, 24] recruited participants only from rehabilitation centres which means this sample may not be relevant to those with minor strokes.

Implications for stroke survivors and clinicians

The three studies in our review that reported the course of fatigue of individuals [23, 25, 27] suggest that if a patient has fatigue shortly after the stroke, he/she is likely to report fatigue in the long term, and if a patient reports no fatigue in the first few weeks after their stroke, he/she is likely to remain non-fatigued. Although a small percentage will develop fatigue at a later stage and a similar percentage will recover from it. Therefore clinicians should consider assessing patients for fatigue whilst an inpatient or shortly after discharge from hospital.

The studies included in this review have demonstrated that fatigue is a problem that affects young as well as older stroke survivors, with the mean (or median) age of participants in eight of the included studies being 65 years or under. For younger stroke survivors fatigue can have very obvious consequences for daily life e.g. caring for children [47], driving a car [46] and returning to paid employment [4, 47]. These factors are very important for the rehabilitation of younger stroke survivors and clinicians and health care workers should aim to ensure that adequate support is made available for these patients in relation to their fatigue.

Implications for research

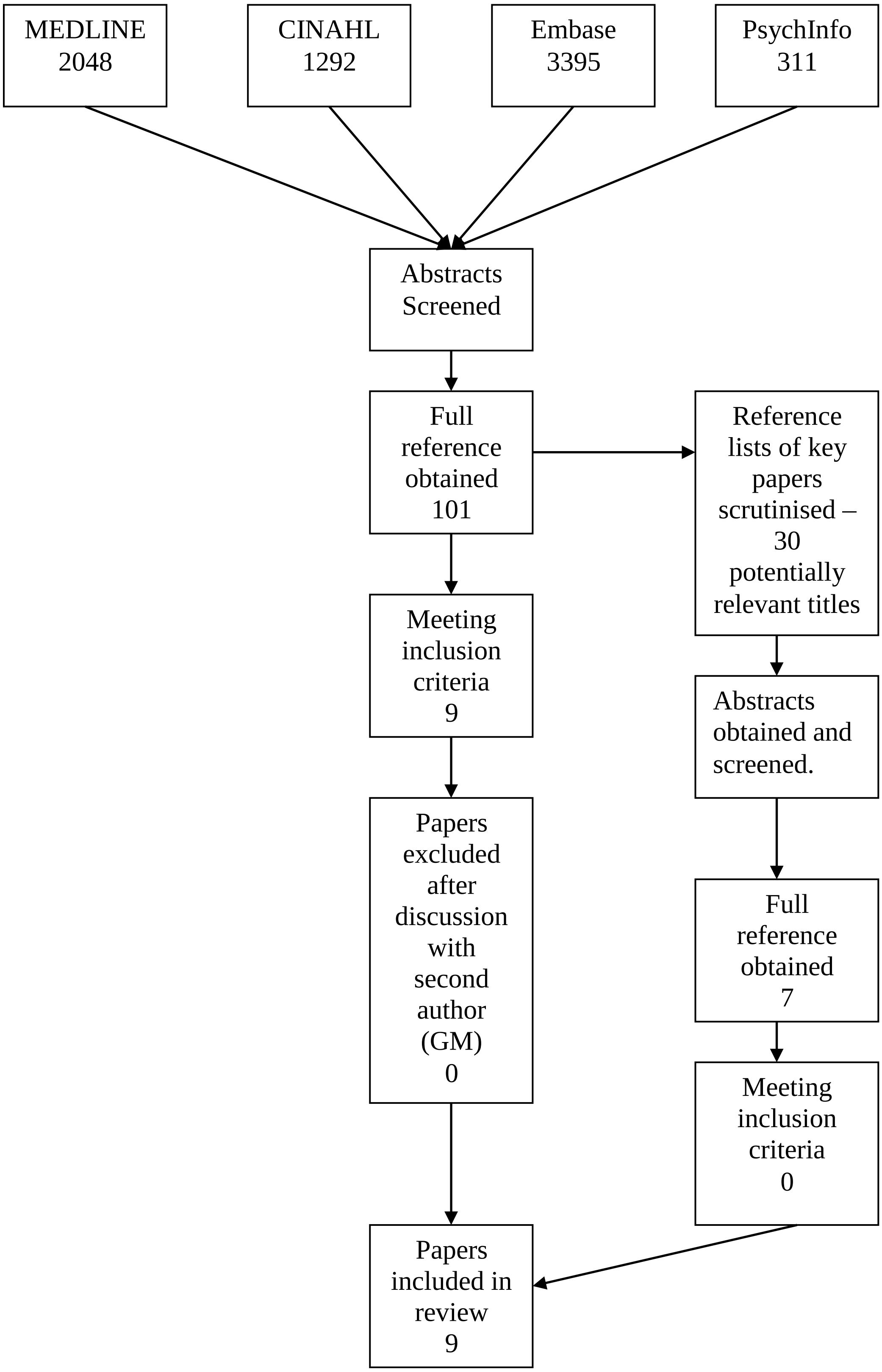
Further longitudinal studies are required with large sample sizes, representative groups of patients and the characteristics of patients lost to follow up being thoroughly reported. These longitudinal studies should assess mood and fatigue at all time points to provide more evidence regarding whether depression may cause fatigue in some patients or vice versa or whether a third factor causes both.

This review has demonstrated the diversity of methods for assessing fatigue. Although some of the methods were very similar and may allow cautious comparisons, others were very different and comparisons may not be very meaningful. It is important that future research reaches a consensus regarding how to assess post-stroke fatigue so that studies can be directly compared.

Considering the high frequency of fatigue and the length of time it persists for, it is vital that more research is carried out on potential interventions for established fatigue and ways in which it might be prevented.

Conclusion

Fatigue is a common symptom post-stroke and is likely to persist in the long term for patients who develop it. This review explored the possibility of depression being a cause of fatigue but found insufficient evidence in the literature. Therefore it is vital for preventative and management strategies to be developed for those suffering from fatigue. For these interventions to be made possible potential causes of post-stroke fatigue must be further investigated.


MEDLINE 2048
CINAHL 1292
Embase 3395
PsychInfo 311
Abstracts Screened
Full reference obtained 101
Reference lists of key papers scrutinised – 30 potentially relevant titles
Meeting inclusion criteria 9
Abstracts obtained and screened.
Papers excluded after discussion with second author (GM) 0
Full reference obtained 7
Meeting inclusion criteria 0
Papers included in review 9

	Source of sample	Pathological Type of Stroke	First or recurrent stroke	Age Mean (SD), Range or median	Gender	Method of assessing fatigue	Time of assessment post stroke and number (N) that completed fatigue measure at each time point.	Frequency of fatigue at each time point (95% CI)*	Differences in fatigue scores across time points (if reported)
Schepers 2006	Rehabilitation Centre	Ischaemic 68.9% Haemorrhagic 31.1%	First	56.4 (11.4)	58.7% Male 41.3% Female	Fatigue Severity Scale	Admission, N=167 6 months, N=167 12 months, N=167	51.5 (43.5-59.5) 64.1 (57.1-71.1) 69.5 (62.5-76.5)	Significantly higher fatigue scores at 1 year than at admission (p<0.000)
Van de Port 2007	Rehabilitation Centre	Ischaemic 72.2% Haemorrhagic 27.8%	First	57.3 (11.1)	59.6% Male 40.4% Female	Fatigue Severity Scale	6 months, N=223 12 months, N=223 36 months, N=223	68 (62-74) 74 (68 – 80) 58 (52- 64)	Not reported
Skaner 2007	Various sources	Ischaemic 78% Haemorrhagic 6% Non-specified stroke 16%	First	73.3 (11.8)	48% Male 52% Female	Single item on Goteborg Quality of Life Instrument	3 months, N=106 12 months, N=97	69 (60 – 78) 58 (48 - 68)	Significantly lower fatigue scores at 1 year than at 3 months. (p=0.044)
Sisson 1995	Three Hospitals	All right hemisphere strokes	First	33-77	46% Male 54% Female	Single question on Neurobehavioural Rating Scale. Mental fatigue	1 month, N=13 6 months, N=13	92.3 (78.3-100) 84.6 (64.6- 100)	Not reported
Christensen 2008	Three acute stroke units	Ischaemic or haemorrhagic	First	Median 64.5 IQR 55.8-72.5	56% Male 44% Female	Multidimensional Fatigue Inventory (MFI-20). General fatigue subscale.	10 days, N=138 3 months, N=138 12 months, N=138 24 months, N=138	59 (51-67) 44 (36 – 52) 38 (30 – 46) 40 (32- 48)	Significantly lower fatigue scores at 3 months than at 10 days (p<0.0001).

									No further significant changes between 3 months and 2 years
Snaphaan 2011	Hospital Neurology Department	Ischaemic	First or recurrent	65 (12.9)	64% Male 36% Female	Checklist Individual Strength Fatigue Subscale	2 months, N=108 18 months, N=108	35 (26-44) 33 (24- 42)	Not reported
Hellawell 1999	Hospital Neurosurgical Unit	Subarachnoid Haemorrhage	Not specified	49.7 (14.6)	45.5 Male 54.5 Female	Single item on Head Injury Symptom Checklist	6 months, N=28 12 months, N=22 24 months, N=19	64.3 (46.3-82.3) 59.1 (38.1-80.1) 68.4 (47.4-89.4)	Not reported
Ogden 1994	Hospital Neurosurgery Unit	Subarachnoid Haemorrhage	First	44.7(14.2) Men 46.4 (12.7) Women	33.7% Male 66.3% Female	Single question – were they more frequently fatigued than before their SAH (yes/no)	10 weeks, N=89 12 months, N=66	88.9 (81.9 – 95.9) 86.2 (78.2-94.2)	Not reported
Noble 2008	Two hospitals	Subarachnoid Haemorrhage	First	52.4	62.9% Male 57.1% Female	Multidimensional Fatigue Symptom Inventory – Short Form	24-251 days (109 average) N= 73 335-672 days (406 average) N = 87	59 (48 – 70) 36 (26 – 46)	No significant differences in fatigue scores between time 1 and time 2 (p>0.05)

Table 1 – Studies assessing fatigue at two or more time points after stroke

Paper	Method of measuring depression and/or anxiety	Method of measuring fatigue	Associations between mood and fatigue after stroke	Additional evidence that depression precedes fatigue.
Schepers 2006	Center of Epidemiologic studies depression scale (CES-D)	Fatigue Severity Scale	Depression at one year is associated with fatigue at one year ($p<0.001$)	None reported
Snaphaan 2011	Hospital Anxiety and Depression Scale (HADS)	Checklist for Individual Strength Fatigue Subscale	Higher levels of depression and anxiety at baseline were significantly associated with fatigue at baseline ($p<0.01$, adjusted for age and gender)	Patients with fatigue at follow up but not at baseline had higher depression scores at baseline than patients without fatigue at both time points. (OR 1.32; 95% CI 1.04-1.69 per each point increase on the HADS depressive symptoms items). Higher levels of depression ($p<0.01$) and anxiety ($p=0.03$) at baseline were significantly associated with fatigue at follow up (adjusted for age and gender)
Noble 2008	Post-traumatic stress diagnostic scale	Multidimensional Fatigue Symptom Inventory	At the first time point, PTSD symptom severity scale scores were significantly associated with total fatigue scores at time point 1(R squared = 0.49, beta=0.786, $p<0.0001$). At the second time point, PTSD symptom severity scale scores were significantly associated with total fatigue scores at assessment 2 (R squared = 0.58, beta = 0.796, $p<0.0001$)	None reported

Table 2 – Longitudinal cohort studies reporting associations between mood and fatigue after stroke.
PTSD = Post Traumatic Stress Disorder

Table 3 – Relevant items on Downs and Black quality assessment checklist and which studies included in our review did not fulfil the item.

Items on checklist relevant to included studies	Studies which did NOT fulfil quality for this item or we were unable to determine from paper.
Reporting Subscale	
Is the hypothesis/aim/objective of the study clearly described?	
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	
Are the characteristics of the patients included in the study clearly described?	
Are the main findings of the study clearly described?	Sisson 1995 [28]
Does the study provide estimates of the random variability in the data for the main outcomes?	Hellawell 1999 [31], Ogden 1994 [29], Sisson 1995 [28], Skaner 2007 [30].
Have the characteristics of patients lost to follow-up been described?	Van de Port 2007 [24], Schepers 2006 [23], Snaphaan 2010 [27], Christensen 2008 [25], Hellawell 1999 [31], Ogden 1994 [29].
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Van de Port 2007 [24], Ogden 1994 [29].
External Validity Subscale	
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Van de Port 2007 [24], Sisson 1995 [28].
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Van de Port 2007 [24], Schepers 2006 [23], Snaphaan 2010 [27], Noble 2008 [26], Hellawell 1999 [31], Sisson 1995 [28]
Internal Validity subscale - bias	
If any of the results of the study were based on "data dredging" was this made clear?	
Were the statistical tests used to assess the main outcomes appropriate?	Sisson 1995 [28]
Were the main outcome measures used accurate (valid and reliable)?	
Internal Validity subscale – confounding (selection bias)	
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Ogden 1994 [29]
Were losses of patients to follow-up taken into account?	Snaphaan 2010 [27], Christensen 2008 [25], Ogden 1994 [29]

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Appendix 2 - Systematic review for the frequency and natural history of fatigue after stroke protocol

Hypothesis: Post stroke fatigue improves during the first year after stroke onset.

Aims:
To determine the frequency of fatigue after stroke.
To determine the natural history of fatigue after stroke.
To determine whether there is a temporal association between fatigue and mood.

Objectives:
To identify all longitudinal cohort observational studies of fatigue after stroke, and report on its frequency, natural history and associations with depression and/or anxiety.
To evaluate study quality, using a checklist for observational studies.

Search Strategy for Review

The databases that will be searched will be MEDLINE, EMBASE, CINAHL, PsycInfo.

The bibliographies of relevant papers will also be searched for references missed by other methods.

Criteria for including studies in this review

Study Characteristics

- Study must be published in a peer review journal.
- The design of the study is observational, either a longitudinal cohort study or a case-control study.
- The study is written in the English language
- Patients must have been recruited and first assessed for fatigue within 6 months of stroke onset.
- Fatigue must have been specifically assessed even if only by asking a single question requiring a YES/NO response
- Fatigue must have been assessed on at least 2 separate occasions (once at recruitment plus 1 follow up or 2 follow ups)
- There should be at least 1 month between assessments of fatigue.

Participant Characteristics

- Any patient clinically diagnosed with a stroke either first ever or recurrent and either an ischaemic or haemorrhagic stroke.
- Study must have retained ten participants or more throughout the study. (if they start with 11 participants and only have 9 by the end of the study then don't include).
- All human stroke patients, over 18 years of age. No upper age limit.
- Studies which focus on multiple aspects of stroke will be included as long as fatigue is specifically assessed.
- Literature that mentions fatigue in stroke patients and that of patients with a traumatic brain injury, Multiple Sclerosis or Parkinson's Disease will also be included provided the data relating to the stroke patients can be extracted separately.

Criteria for excluding studies from this review

- Cross sectional, experimental, quasi-experimental papers or studies that involve an intervention.

- Papers that only assess fatigue at one time point
- Papers only published in abstract form
- If the population of the study is people with depression or sleep apnoea as opposed to the general stroke population.
- Studies where participants have been recruited retrospectively
- Papers with an unstructured assessment of fatigue e.g. (e.g. qualitative assessments of fatigue where the specific questions asked may have varied from patient to patient)
- Studies of mixed populations unless separate results for stroke patients can be identified.
- If the study includes patients who are clinically diagnosed as having a Transient Ischemic Attack (T.I.A.) rather than a stroke. Unless data from the stroke patients can be separately identified and extracted.

Assessing the Quality of Papers

Included papers will be quality assessed by using the Downs and Black (1998) checklist.

Data Analysis

The intention is to use Revman software to create summary statistics such as the proportion of participants with fatigue at each time point with confidence intervals.

If this is not possible due to included studies being too heterogeneous, then data synthesis will take a narrative approach. This will involve presenting all the results together in a clear descriptive summary table, analysing the relationships within and between studies in order to evaluate the evidence that each study provides for the hypothesis.

Data Extraction

Two authors will independently extract data and will resolve any discrepancies or uncertainties with Professor Gillian Mead.

Appendix 3 - Search Strategy for Literature Review and the Systematic review of the frequency and natural history of fatigue after stroke.

MEDLINE Search Strategy

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischaemia/ or exp carotid artery diseases/ or cerebrovascular accident/ or exp brain infarction/ or exp cerebrovascular trauma/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or intracranial arteriovenous malformations/ or exp "Intracranial Embolism and Thrombosis"/ or exp intracranial hemorrhages/ 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 hemataoma$ or bleed$)).tw
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw
7. 1 or 2 or 3 or 4 or 5 or 6
8. fatigue/ or fatigue syndrome, chronic/ or asthenia/ or mental fatigue/ or muscle fatigue/ or lethargy/
9. (fatigue$ or asthenia$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg$ or apath$ or malaise).tw
10. ((low or lack) adj5 energy).tw
11. 8 or 9 or 10
12. 7 and 11

EMBASE Search Strategy

1. cerebrovascular disease/ or basal ganglion hemorrhage/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or exp carotid artery disease/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/
2. stroke unit/ or stroke patient/
3. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or aploplex$ or SAH).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw
5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw
6. hemiplegia/ or paresis/
7. (hemipleg$ or hemipar$ or paresis or paretic).tw
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. fatigue/ or chronic fatigue syndrome/ or exhaustion/ or lassitude/ or muscle fatigue/
10. lethargy/ or listlessness/ or malaise/ or apathy/ or dysthymia/ or asthenia/ or neurasthenia/
11. (fatigue$ or astheni$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or exhaustion or lassitude or listlessness or letharg$ or apath$ or malaise).tw
12. ((low or lack) adj5 energy).tw
13. 9 or 10 or 11 or 12
14. 8 and 13
15. limit 14 to human
16. (hepatitis or dialysis or cancer or carcinoma or meningitis or heat stroke or cerebral palsy).ti
17. (Parkinson$ or sclerosis or myeloma or tumor$ or tumour$ or transplant$).ti
18. exp neoplasm
19. (kidney or renal or heat or cardiac or migraine).ti
20. 16 or 17 or 18 or 19

21. 15 not 20

PsycInfo Search Strategy

1) cerebrovascular disorders/ or cerebral hemorrhage/ or cerebral ischemia/ or cerebrovascular accidents/
2) (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplexy$ 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 intracran$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw
5) Hemiplegia/
6) (hemipleg$ or hemipar$ or paresis or paretic).tw
7) 1 or 2 or 3 or 4 or 5 or 6
8) Fatigue/ or chronic fatigue syndrome/ or hypersomnia/ or sleepiness/ or asthenia/ or neurasthenia/ or apathy/ or dysthymic disorder/
9) (fatigue$ or asthenia$ or neurastheni$ or tired or tiredness or weary or weariness or exhausted or lassitude or letharg$ or apath$ or malaise).tw
10) ((low or lack) adj5 energy).tw
11) 8 or 9 or 10
12) 7 and 11

CINAHL Search Strategy

1. MH "Cerebrovascular Disorders+") OR (MH "Carotid Artery Diseases+") OR (MH "Carotid Artery Dissections") OR (MH "Cerebral Arterial Diseases+") OR (MH "Intracranial Arterial Diseases+") OR (MH "Arterial Occlusive Diseases+") OR (MH "Cerebral Aneurysm") OR (MH "Intracranial Embolism and Thrombosis+") OR (MH "Cerebral Ischemia+") OR (MH "Hypoxia-Ischemia, Brain") OR (MH "Stroke") OR (MH "Stroke Patients") OR (MH "Stroke Units") OR (MH "Cerebral Vasospasm") OR (MH "Intracranial Hemorrhage+") OR (MH "Subarachnoid Hemorrhage") OR (MH "Basal Ganglia Hemorrhage") OR (MH "Vertebral Artery Dissections") OR (MH "Cerebral Hemorrhage+") OR (MH "Basal Ganglia Cerebrovascular Disease+") OR (MH "Basal Ganglia Diseases+") OR (MH "Arteriovenous Malformations+")

2. TX stroke or TX poststroke or TX post-stroke or TX cerebrovasc* or TX brain vasc* or TX cerebral vasc* or TX cva* or TX apoplex* or TX SAH

3. TX brain* n5 isch?emi* or TX brain* n5 infarct* or TX brain* n5 thrombo* or TX brain* n5 emboli* or TX brain* n5 occlus*

4. TX cerebr* n5 isch?emi* or TX cerebr* n5 infarct* or TX cerebr* n5 thrombo* or TX cerebr* n5 emboli* or TX cerebr* n5 occlus*

5. TX cerebell* n5 isch?emi* or TX cerebell* n5 infarct* or TX cerebell* n5 thrombo* or TX cerebell* n5 emboli* or TX cerebell* n5 occlus

6. TX intracran* n5 isch?emi* or TX intracran* n5 infarct* or TX intracran* n5 thrombo* or TX intracran* n5 emboli* or TX intracran* n5 occlus*

7. TX intracerebral n5 isch?emi* or TX intracerebral n5 infarct* or TX intracerebral n5 thrombo* or TX intracerebral n5 emboli* or TX intracerebral n5 occlus*

8. TX brain* n5 haemorrhage* or TX brain* n5 hemorrhage* or TX brain* n5 haematoma* or TX brain* n5 hematoma* or TX brain* n5 bleed*

9. TX cerebr* n5 haemorrhage* or TX cerebr* n5 hemorrhage* or TX cerebr* n5 haematoma* or TX cerebr* n5 hematoma* or TX cerebr* n5 bleed*

10. TX cerebell* n5 haemorrhage* or TX cerebell* n5 hemorrhage* or TX cerebell* n5 haematoma* or TX cerebell* n5 hematoma* or TX cerebell* n5 bleed*

11. TX intracerebral n5 haemorrhage* or TX intracerebral n5 hemorrhage* or TX intracerebral n5 haematoma* or TX intracerebral n5 hematoma* or TX intracerebral n5 bleed*

12. TX intracranial n5 haemorrhage* or TX intracranial n5 hemorrhage* or TX intracranial n5 haematoma* or TX intracranial n5 hematoma* or TX intracranial n5 bleed*

13. subarachnoid n5 haemorrhage* or subarachnoid n5 hemorrhage* or subarachnoid n5 haematoma* or subarachnoid n5 hematoma* or subarachnoid n5 bleed*

14. (MH "Hemiplegia")

15. TX hemipleg* or TX hemipar* or TX paresis* or TX paretic*

16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. (MH "Fatigue+") OR (MH "Fatigue (Saba CCC)") OR (MH "Fatigue Syndrome, Chronic") OR (MH "Muscle Fatigue") OR (MH "Fatigue (NANDA)")

18. (MH "Asthenia")

19. TX fatigue* or TX astheni* or TX neurastheni* or TX tired or TX tiredness or TX weary or TX weariness or TX exhaust* or TX lassitude or TX listlessness or TX letharg* or TX apath*

20. TX malaise

21. TX low n5 energy or TX lack n5 energy

22. 17 or 18 or 19 or 20 or 21

23. 16 and 22

Appendix 4 - Data Extraction Form

This was completed for all potentially relevant papers

Date of data extraction:

Identification features of the study
Record number (to uniquely identify study):
Author:

Article title:

Citation:
Type of publication (e.g. journal article, conference abstract):
Country of origin:
Source of funding:

Study Characteristics

Aims/ objectives of the study:

Study design:

Study inclusion and exclusion criteria:

Recruitment procedures used (consecutive patients, convenience sampling, retrospective recruitment):

How is fatigue being measured?
Has fatigue been separately assessed?
How is the study defining fatigue?

Number of times fatigue has been separately assessed:
Time between assessments of fatigue (length of follow up):

How is mood being measured?

How much time after stroke are measurements of mood being taken?

Participant Characteristics

How have they defined the study population. (e.g. stroke patients, people over 65, people with depression):

Total number of participants recruited to study:
Total number of participants at end of study:
Number of participants who died before end of study:
Number of participants who dropped out or were lost to follow-up before end of study:
Characteristics of those who dropped out:

Age:
Age limits used in the study:
Gender:
First or recurrent stroke:
Depression before stroke (if mentioned):

Ethnicity:

Socio-economic status:
Type of stroke:
Stroke subtype:
Stroke severity measure and score:
Co-morbidities:

Outcome data/ results

Can fatigue data for stroke patients be extracted separately from other types of patients?
Has fatigue data been reported?
Cut off score used:
Percentage reported as fatigued:

Has depression data been reported?
Cut off score used for depression
Percentage reported as depressed:
Measurement tools or methods used for measuring fatigue and/ or depression

Were participants put into subgroups (i.e. age groups, stroke subtype groups).
What were the groups (i.e. under 65, 65 – 80, 80+).

For each subgroup (if appropriate)
Number of participants recruited:
Number of participants included in analysis:
Number of withdrawals, exclusions, lost to follow up:

Summary outcome data (extract for each subgroup)

Dichotomous	Number with fatigue/depression:
	Number without fatigue/depression:
Continuous	Mean and SD of fatigue scale (whichever is used).
	Mean and SD of depression measure (i.e. HADS,)

Methods of statistical analysis including variables adjusted for:

Results of study analysis (extract for each patient sub-group)
Dichotomous p-value, confidence intervals

Continuous mean difference, confidence intervals, Pearson's or Spearman's r value, regression analysis:

Details of any additional relevant outcomes reported:

Amount of missing data and which methods (if any) were used to deal with it:

Appendix 5 - Published paper "Fatigue after stroke: a systematic review of associations with impaired physical fitness"

The full reference for this paper is: Duncan F., Kutlubaev M.A., Dennis M.S., Greig C., and Mead G.E. (2012) Fatigue after stroke: a systematic review of associations with impaired physical fitness. *International Journal of Stroke*. 7(2), pp 157-162.

Abstract

Background: Fatigue is a common and distressing symptom after stroke. One important hypothesis is that fatigue after stroke might be triggered by physical de-conditioning which sets up a vicious, self-perpetuating cycle of fatigue, avoidance of physical activity, further de-conditioning and more fatigue. If an association between physical activity and fatigue after stroke could be established this would provide a rationale for developing a physical activity based treatment.

Aims: to systematically review all observational studies which have measured both fatigue post stroke *and* one or more measures of physical fitness and/or physical activity at the same time point and reported the association between fatigue and fitness variables.

Method: Publications were identified by systematically searching databases MEDLINE, EMBASE, CINAHL, PsycInfo and Sportdiscus using keywords “fatigue”, “stroke”, “fitness” or “activity” and their associated terms or synonyms. Publications that provided data on associations between fatigue in stroke patients and levels of physical activity, cardio-respiratory fitness and/or muscle strength and mass were included.

Results: Twenty nine potential studies were retrieved after scrutinising the titles and abstracts, of which only three fulfilled our inclusion criteria. No association between fatigue and any measures of physical activity or fitness were found. One study did find, through structural equation modelling techniques that fatigue indirectly influences exercise through self efficacy expectations.

Conclusions: there is very limited evidence regarding associations between exercise, fitness and fatigue after stroke. It still remains highly plausible that exercise can have a positive influence on fatigue. Future research should be longitudinal in design.

Introduction

Fatigue is a common and distressing symptom after stroke. For example, one study found that 40% of stroke patients felt that fatigue was either their worst symptom or one of their worst symptoms (1). Fatigue may interfere with physiotherapy sessions (2) and can negatively affect stroke survivors' physical and psychological functioning (1). One study showed that fatigue is an important predictor for death 2-3 years after stroke onset even after depression had been taken into account (3). The reason why fatigue is associated with reduced survival is not known. The frequency of fatigue after stroke is reported as 30 to 68% depending upon whether depression is taken into account (1-8). The aetiology of fatigue after stroke is currently unknown but is likely to be a multidimensional construct involving both biological and psychological elements.

After stroke, there is often a sudden reduction in physical activity as a direct result of neurological impairments. This physical inactivity may lead to decline in physical fitness. One important hypothesis that needs exploring is that fatigue after stroke might be triggered by physical de-conditioning which occurs soon after stroke onset. Several studies have shown that limb muscle strength (an important component of physical fitness) on both sides is significantly lower in patients after stroke compared with controls (9). Another study demonstrated that the quadriceps strength of the leg unaffected by the stroke declined by 30% as early as the first 7 days after stroke (10). This reduction in muscle strength may increase the amount of effort required to carry out daily tasks and therefore induce fatigue. Patients may then avoid further activity, thus setting up a vicious, self-perpetuating cycle of fatigue, avoidance of physical activity, further de-conditioning and more fatigue.

In cancer patients, muscle de-conditioning has previously been found to be associated with fatigue (11). The role of muscle deconditioning in *causing* cancer fatigue is supported by the observation that a combination of resistance and aerobic training significantly reduced sensory, affective, cognitive/mood, behavioural and total fatigue (12). It is not yet known if muscle de-conditioning is associated with fatigue in stroke patients. Given that physical activity levels (13), and aerobic fitness

(14) are low after stroke it is biologically plausible that fatigue after stroke might be related to physical de-conditioning and reduced physical activity. Establishing an association would provide a rationale for developing a physical activity based treatment for fatigue after stroke. Clearly, demonstrating an association does not necessarily imply causation (because fitness levels may be reduced because people with fatigue avoid activity), but it is necessary to seek one in order to provide a rational basis for starting to develop exercise interventions for fatigue after stroke.

The aim of this systematic review was to identify all cross sectional and longitudinal observational studies which measured both fatigue post stroke *and* one or more measures of physical fitness and/or physical activity at the same time point and reported the association between fatigue and fitness variables.

Method

Procedure

Searches were conducted in MEDLINE (from 1966), EMBASE (from 1980), CINAHL (from 1937), PsycInfo (from 1806) and Sportdiscus (from 1800) on 4th November 2010 using the keywords "fatigue", "stroke", "fitness" or "activity" and their associated terms or synonyms.

Potentially relevant papers were identified from their title and abstract and exported to Endnote. After duplicates were removed, one author (FD) read every abstract and obtained the full text of papers that potentially met the inclusion criteria. Reference lists of the retrieved articles were scrutinised for further potentially relevant studies. One reviewer (FD) applied the following inclusion criteria to the retrieved articles: 1) written in English 2) published in a peer reviewed journal 3) recruited people with stroke (first or recurrent, ischaemic or hemorrhagic) > 18 years 4) retained 10 or more participants 5) specifically assessed the presence or absence of fatigue using a single question, a case definition or a specified cut-off on a fatigue scale; or reported fatigue scores as a continuous variable and 6) provided data on associations between fatigue in stroke patients and levels of physical activity, cardio-respiratory fitness and/or muscle strength and mass. Any disagreement about inclusion was discussed with both second reviewers (GM and MK).

Papers were excluded if: 1) they were only published in abstract form 2) they contained no primary data (e.g. reviews, editorials etc) 3) it was not possible to separately extract data for stroke patients from other types of patient.

Data extraction – Two reviewers (FD and MK) independently extracted data (onto paper data collection forms) describing a) age, gender, sample size, time since stroke, type of stroke. b) method(s) of measuring fatigue c) method(s) of measuring physical activity and/ or fitness d) results of fatigue and physical fitness and physical activity measures and e) any association reported between fatigue and either physical activity or physical fitness.

Data synthesis – we intended to perform a meta-analysis to synthesise the relative risks but the data were too diverse to allow for this. Instead we opted for a narrative data synthesis approach

Definitions

For this review we were looking for associations between amount of physical activity performed by a stroke survivor and not papers that reported activity limitations. We are defining physical activity as "all bodily movement that is produced by the contraction of skeletal muscle and that substantially increases energy expenditure". (30, 31) For instance, we included studies that reported stroke survivors' walking, running, cycling, swimming, playing sports, housework or gardening but excluded studies that used gait or changes in gait patterns, single limb activity, sitting to standing, toileting or bathing or weight bearing therapy as measures of physical activity. We also excluded studies where activity was measured by an activities of daily living scale such as the Nottingham Activities of Daily Living scale (32) or the Frenchay Activities Index (33) as several items on these scales refer to activities which do not meet our definition of physical activity such as reading books, writing letters, driving a car, taking a car ride or participating in gainful work.

We are defining physical fitness as "the collective term for a set of physiological attributes which people have or achieve which determine the ability to perform physical activity."(30, 31) These attributes include cardio-respiratory fitness, muscle strength and muscle power. Physical activity and physical fitness correlate positively with each other (30). The distinction between the two constructs is that fitness is a condition that a person can be in at a point in time and activity is an energy-consuming process. (34)

Fatigue was defined as a subjective feeling of lack of energy, weariness and aversion to effort (35). For this review we were interested in chronic fatigue so we included studies that used a questionnaire that had been specifically developed to measure fatigue or tiredness in daily life. We excluded studies where muscle or exertion fatigue was measured in participants directly after they completed a specific fatigue inducing exercise.

An observational study was defined as any study where no intervention took place. However papers were included if both post-stroke fatigue and one or more measures of physical fitness and/or physical activity were taken and reported at the baseline of an intervention study.

We are hypothesising that if a stroke survivor increases their levels of physical fitness and/or activity then this will reduce fatigue levels. Therefore the independent variable in this review is fitness/ activity and the dependent variable is fatigue. However we do recognise that this may not be the direction of causality. It is also plausible that higher fatigue levels lead to less activity and / or fitness.

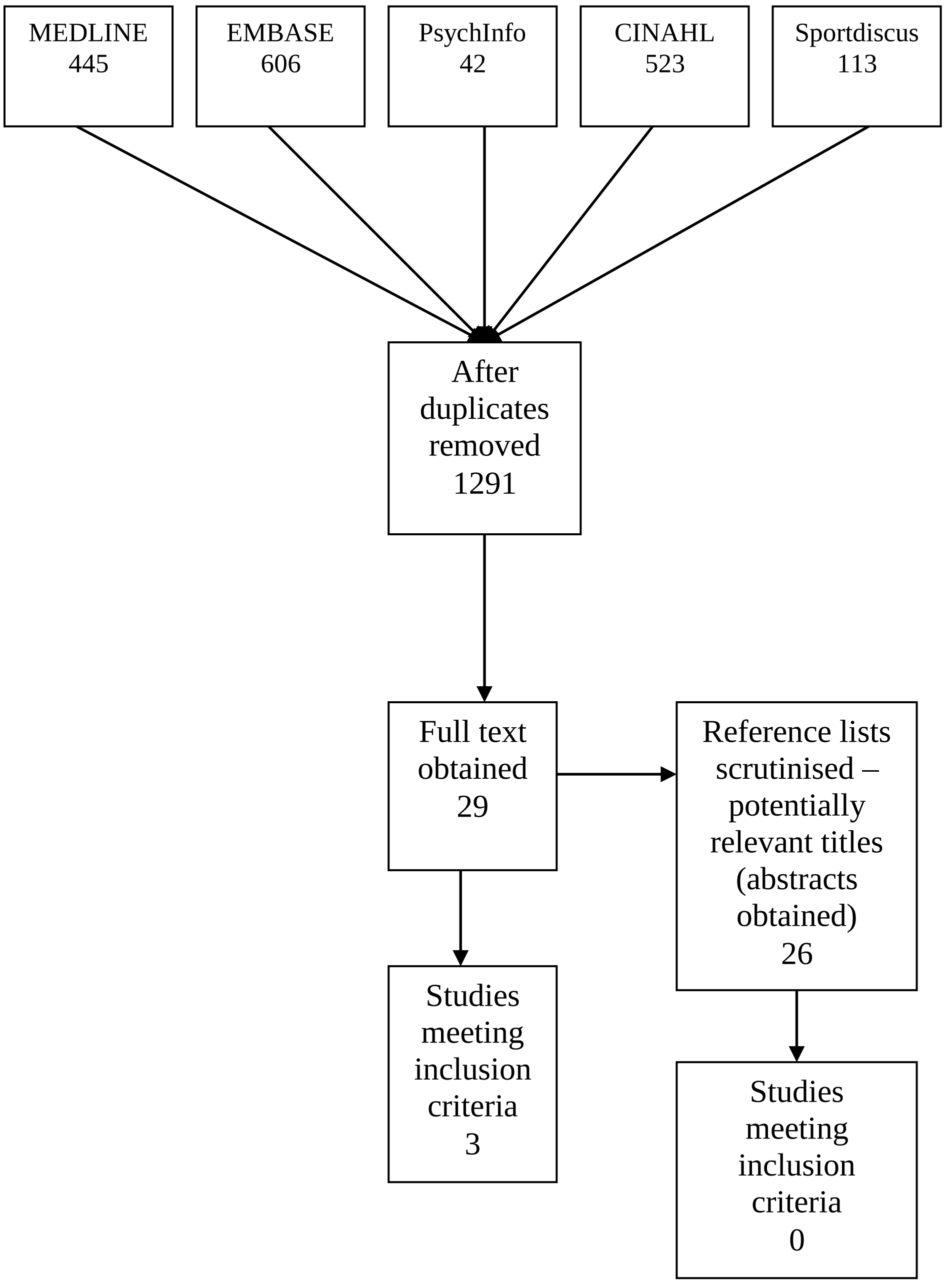
Results

The electronic search identified 1291 citations, after Endnote had removed duplicates. 29 full texts were retrieved, of which, three papers, recruiting a total of 444 participants, fulfilled inclusion criteria (figure 1). Scrutiny of reference lists provided no further papers for inclusion. The main reasons for excluding a study were; a) review with no primary data b) fatigue was not measured or c) the type of activity measured did not meet the inclusion criteria, for example measured gait patterns, single limb activity or participants self-reported *ability* to walk in the community (as opposed to quantity of activity).

All three eligible studies were cross-sectional (15-17) two included only ischaemic strokes (15,16) and one included “any stroke survivor” (17). Mean participant age was 59 years to 66 years. In two studies (15,16) the participants were all community dwelling and were able to walk with or without a walking aid. In one study (17), participants were either attendees of a National Stroke Association support group or participated in the study by completing a questionnaire online.

The Fatigue Severity Scale (FSS) was used as the measure of fatigue in two of the studies. Mean FSS scores were reported as 3.9 (15) and 3.28 (16) with 46% and 42% categorised as fatigued using a average score of > 4 as a cut off. In one study, (17) 68% either agreed or strongly agreed that fatigue influenced their daily activities.

Figure1


MEDLINE
445
EMBASE
606
PsychInfo
42
CINAHL
523
Sportdiscus
113
After duplicates removed
1291
Full text obtained
29
Reference lists scrutinised – potentially relevant titles (abstracts obtained)
26
Studies meeting inclusion criteria
3
Studies meeting inclusion criteria
0

Association between physical fitness and fatigue

Two studies (15,16) investigated whether there was an association between economy of gait (rate of oxygen consumption, $\dot{V}O2$), peak exercise capacity ($\dot{V}O2$ peak) and fatigue. Both studies found no association between fatigue and these measures of cardiovascular fitness (Table 1).

Association between physical activity and fatigue

All three included studies explored the relationship between one form of physical activity and fatigue. One study measured participant's daily step count (15), another study measured the intensity of ambulatory activity by recording the number of steps per minute (16), in a third study (17) participants indicated through a single question how many times a week they participated in a physical activity of at least 20 minutes duration that caused sweating or increases in respiratory or heart rate.

No association between fatigue and any of the measures of physical activity was found (Table 1). One study did find, through structural equation modelling techniques, that fatigue indirectly influences exercise through self efficacy expectations.

Discussion

This is, to our knowledge, the first systematic review of studies that has investigated associations between physical fitness, physical activity and post-stroke fatigue. We found only three studies which met our inclusion criteria. These studies were cross-sectional, observational studies. Two used the FSS, one used both the FSS and a visual analogue scale and one measured fatigue with a single question with a five point Likert response scale. Physical activity and fitness were measured in different ways.

None of these studies found a statistically significant direct relationship between post-stroke fatigue and either physical fitness or physical activity. One study, however, did find that participants with higher levels of fatigue were more likely to have lower self-efficacy expectations for exercise and therefore were less likely to participate in physical activity.

Therefore there is limited evidence regarding an association between post-stroke fatigue and either exercise or physical fitness. In light of this lack of evidence there is a need for further research as it still remains highly plausible that exercise can have a positive influence on fatigue. Exercise is reported to be the most effective non-pharmacologic intervention for cancer related fatigue (20) and there is some evidence that exercise may reduce fatigue in people with Multiple Sclerosis (18, 19) although another study found exercise to have no effect on fatigue levels of MS patients (36)

There are multiple mechanisms by which exercise may plausibly improve post-stroke fatigue. For instance, physical exercise can increase cerebral blood flow by activating the sympathetic nervous system (21). Central command during exercise independently increases regional cerebral blood flow in insular and anterior cingulated cortices (22) and ischaemic damage to these areas is associated with the development of tiredness (23). Development of fatigue in people with multiple sclerosis correlates with atrophy of frontal and posterior parietal cortices (24), while aerobic fitness reduces tissue loss in these areas of the brain in aging humans (25). On a molecular level, physical exercise may change the functioning of neurotransmitters which may lead to the development of fatigue (26). Finally a lack of physical activity may cause alterations in the synthesis of muscle derived ll-6 and this may also contribute to the development of fatigue (27).

Shortly after the searches for this review were carried out, a cross-sectional study that meeting our inclusion criteria was published (28). Participants were recruited from local stroke support groups and a research participant database and were between 6 months and 5 years post-stroke. Fitness was measured using a maximal effort graded exercise test ($\dot{V}O2$ peak) using a stepping ergometer. This study postulated that there are two distinct types of fatigue; exertion fatigue and chronic fatigue. Exertion fatigue was measured using a Visual Analogue Fatigue Scale and chronic fatigue using the

Fatigue Severity Scale (FSS). Higher fitness ($\dot{V}O2$ peak) was significantly associated with less exertion fatigue ($r=-0.582$, $p<0.01$) but like the other studies identified in this review, they found no association was shown between fitness and chronic fatigue. This study suggests that exercise may have a positive effect on some aspects of a stroke patient's experience of tiredness but does not provide a complete solution.

Currently there is a randomised controlled trial running in the Netherlands investigating whether a new treatment programme, Cognitive and Graded Activity Training (COGRAT) can have an effect on post-stroke fatigue compared with cognitive training alone or no treatment. This intervention consists of 12 weeks of Cognitive Behavioural Therapy (CBT) combined with endurance, strength and flexibility training. Preliminary results from 40 participants have shown this treatment programme to significantly reduce fatigue severity as measured using the Checklist Individual Strength fatigue scale ($p< 0.001$). The effect was evident on both post-treatment and 6 month follow up assessments (29).

Future studies should be longitudinal in design in order to start to elucidate temporal associations between fatigue and fitness i.e. does reductions in fitness generally precede post-stroke fatigue, or does post-stroke fatigue generally pre-date reductions in fitness. Measures of aerobic fitness, daily activity and muscle strength should be objective rather than self report. It could be investigated whether certain types of exercise are more likely to influence fatigue. It should also be recognised that there may not be a direct cause and effect relationship between fatigue and physical fitness and/or activity. For instance one of the studies included in our review (17) found that fatigue only had an influence on exercise when self efficacy expectations were taken into account. In a similar vein another study found the relationship between fatigue and instrumental activities of daily living was confounded by depression (37). Therefore future research should take into account variables such as depression, self efficacy expectations, gender and age as covariates in regression modelling when investigating the relationship between fatigue and physical activity and/or physical fitness.

The strengths of the review include a thorough search strategy and independent data extraction by two authors (FD and MK). The limitations are that we included only papers published in English which may have led to the exclusion of relevant studies published in other languages and we did not do a methodological screening of the included studies.

All three studies included in this review contained limitations. For example: two included small samples sizes (n=53 & 79); one study only used a single question to measure fatigue (17) and in two studies participants had volunteered themselves for the exercise program (15,16). In addition the majority of participants in one study (17) were white, female and unmarried (and so unrepresentative of stroke survivors);

Conclusion

In conclusion there is insufficient evidence of an association between post-stroke fatigue and either physical fitness or physical activity. However it still remains highly plausible that exercise could be an effective treatment for fatigue.

Table 1 - Studies reporting an association between post-stroke fatigue and either physical fitness or physical activity.

Date	Author	Title	Aims and Objectives	Study Design	Time post stroke	Evaluation of fatigue	Measure(s) of physical activity or physical fitness	N	Association between fatigue and physical activity and/or fitness
2006	Michael, Allen & Macko	Fatigue after stroke: Relationship to Mobility, Fitness, Ambulatory Activity, Social Support and Falls Efficacy	To explore the relationships between fatigue, cardiovascular fitness, mobility deficit severity, ambulatory activity patterns, social support and self efficacy for falls.	Observational, cross sectional	6-166 months (mean 10.3)	Fatigue Severity Scale (FSS) paired with a visual analogue scale (VAS)	Economy of gait, peak exercise capacity (V02 peak), ambulatory activity (steps per 24hours).	53 (58.5% male)	No significant differences between fatigued and non-fatigued groups in the fitness measures of economy of gait and V̇O2 peak and ambulatory activity. Steps per 24 hours in those with fatigue 2696 (SD 1524) Steps per 24 hours in those without fatigue 2751 (SD 1528) Economy of gait with fatigue – 8.8 ml/kg/min (SD 1.67) Economy of gait without fatigue – 8.6 ml/kg/min (SD 1.88) V̇O2 Peak with fatigue – 11.34 ml/kg/min (SD 3.04) V̇O2 Peak without fatigue – 11.69 ml/kg/min (SD 2.83) When using the FSS as a continuous variable, linear regression showed that economy gait, V̇O2 peak and ambulatory activity are not significant predictors of fatigue severity.
2007	Michael & Macko	Ambulatory Activity Intensity Profiles,	To describe household and community ambulatory activity	Observational, cross sectinal	6-166 months (mean 10.3)	Fatigue Severity Scale (FSS)	Daily step count and intensity of ambulatory activity: Low intensity <16 steps per minute	79 (53% male)	No significant associations between fitness, step activity and fatigue. Correlation between step intensity and fatigue

		Fitness and Fatigue in Chronic Stroke	profiles in terms of step counts & step intensity levels. To determine whether these profiles are related to fitness or self-reported fatigue				Medium intensity ≥16 and < 30 steps per minute High intensity ≥30 steps per minute. Economy of gait Peak exercise capacity (V̇O2 peak)		Step Intensity Pearson's r Low 0.093 Medium 0.167 High 0.073
2006	Shaughnessy, Resnick & Macko	Testing a Model of Post-Stroke Exercise Behavior	To test a theoretical model of physical activity in stroke survivors	Survey cross-sectional by postal and online questionnaire.	60.2 months	Single question: "Does fatigue influence daily activities" with five point likert response scale	Single question "how often do you engage in activity/exercise?" Response options: never, less than once per week, 1-3 times per week, 4 or more days per week. Activity/ exercise was defined as participation in a physical activity of at least 20 minutes duration that caused sweating or increases in respiratory or heart rate	312 (41% Male)	No significant association between self reported exercise behaviour and fatigue. Structural equation modelling techniques showed that fatigue indirectly influenced exercise through self efficacy expectations.

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Appendix 6 - Systematic review for fatigue after stroke and its associations with physical fitness and/or physical activity protocol

Hypotheses:
Post stroke fatigue is less common in patients who are more physically fit
Post stroke fatigue is less common in patients who are more active.

Aims:
To determine if there is an association between post stroke fatigue and lower levels of physical activity
To determine if there is an association between post stroke fatigue and lower levels of physical fitness.

Objectives:
To identify all cross sectional and longitudinal observational studies which have separately measured both fatigue post stroke and one or more measures of physical fitness and/or activity.
To identify whether any associations exist between these measures.
To report the different methods used to measure physical fitness and activity.

Search Strategy

The databases to be searched will be MEDLINE, EMBASE, CINAHL PsycInfo and SportDiscus.

The bibliographies of relevant papers will also be searched for references missed by other methods.

Review Inclusion Criteria

Study Characteristics

- Study must be published in a peer review journal
- The design of the study is observational (longitudinal cohort studies, cross sectional, case-control studies, case series), experimental (RCT), quasi-experimental (non-randomised controlled studies, before-and-after study, interrupted time series)
- The study is written in the English language
- Fatigue must have been specifically assessed even if only by asking a single question requiring a YES/NO response

Participant Characteristics

- Any patient clinically diagnosed with a stroke either first ever or recurrent and either an ischaemic or haemorrhagic stroke.
- Study must have retained ten participants or more throughout the study. (if they start with 11 participants and only have 9 by the end of the study then don't include).
- All human stroke patients, over 18 years of age. No upper age limit.
- Studies which focus on multiple aspects of stroke will be included as long as fatigue is assessed specifically.
- Literature that mentions fatigue in stroke patients and that of patients with a traumatic brain injury, Multiple Sclerosis or Parkinson's Disease will also be included provided the data relating to the stroke patients can be extracted separately.

Activity Characteristics

- Whole body activity in stroke patients measured by appropriate activity scales, observational techniques or techniques not mentioned in the exclusion criteria.
- Studies measuring cardio-respiratory fitness

- Studies measuring muscle strength and/or mass
- Studies measuring the psychosocial effects of activity in stroke patients
- Literature using the following techniques will be included as long as participants took part in more than one session: fitness training, interventions using treadmills, treadmill training regimes, strength training.

Criteria for excluding studies from this review

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- Papers only published in abstract form
- If the population of the study is people with depression or sleep apnoea as opposed to the general stroke population.
- Studies where participants have been recruited retrospectively
- Papers with an unstructured assessment of fatigue e.g. (e.g. qualitative assessments of fatigue where the specific questions asked may have varied from patient to patient)
- Studies of mixed populations unless separate results for stroke patients can be identified.
- If the study includes patients who are clinically diagnosed as having a Transient Ischemic Attack (T.I.A.) rather than a stroke. Unless data from the stroke patients can be separately identified and extracted.

Activity Characteristics

- Literature using gait or changes in gait patterns
- Single limb activity and sitting to standing as measures of activity
- Papers that reported activities of daily living such as toileting and bathing
- Constraint induced physical therapy
- Weight bearing therapy
- Exercises as part of the patient's usual physiotherapy.
- We are researching <u>chronic</u> fatigue, so also exclude any study that only asks patients about fatigue immediately after doing an exercise intervention regarding how they feel at that moment. (If the study also asks participants how they usually feel or if they have a general problem with fatigue or how they feel over past week or month then include).

<u>Assessing the Quality of Papers</u>

Included papers will be quality assessed by using checklists such at the one created by Downs and Black (1998).

<u>Analysing the Data</u>

The intention is to use Revman software to create summary statistics for the review. These will include statistics on the proportion of participants with fatigue in high or low fitness/ activity groups will be presented along with confidence intervals. Associations will be represented graphically using forest plots.

If this is not possible then data synthesis will take a narrative approach. This will involve presenting all the results together in a clear descriptive summary table, analysing the relationships within and between studies in order to evaluate the evidence that each study provides for our hypotheses.

<u>Data Extraction</u>

Two review authors will check the data extraction and resolve any discrepancies or uncertainties by discussion or clarification with Dr Gillian Mead.

Appendix 7 - Search strategy for systematic review of fatigue after stroke and its associations with physical fitness and/or physical activity.

MEDLINE Search Strategy

The following search strategy will be added on to the strategy used in the review of the frequency and natural history of fatigue after stroke

2. physical fitness/ or recreation/ or exercise/ or leisure activities/ or sports medicine/ or exercise test/ or muscle strength/ or exercise therapy/ or exercise tolerance/ or exertion/ or physical endurance/ or physical therapy/ or locomotion/ or early ambulation
3. sports/ or weight lifting/ or bicycling/ or running/ or swimming/ or walking/ or sports equipment
4. isometric contraction/ or isotonic contraction
5. (physical adj5 (exercise$ or conditioning or activit$ or fitness or therap$)).tw
6. (exercise adj5 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regime$)).tw
7. (fitness adj5 ((train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regime$)).tw
8. ((training or conditioning) adj5 (intervention$ or protocol$ or program$ or activit$ or regime$)).tw
9. (sport$ or recreation$ or leisure or cycl$ or bicycle$ or treadmill$ or run$ or swim$ or walk$).tw
10. ((endurance or aerobic or cardio$) adj5 (fitness or train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regime$)).tw
11. (muscle strengthening or progressive resist$).tw
12. ((weight or strength$ or resistance) adj5 (train$ or lift$ or exercise$)).tw
13. ((isometric or isotonic or eccentric or concentric) adj5 (contraction$ or exercise$)).tw
14. (muscle$ adj5 (conditioning or deconditioning or fitness)).tw
15. (idleness or immobility or inactivity).tw

EMBASE Search Strategy

The following search strategy will be added on to the strategy used in the review of the frequency and natural history of fatigue after stroke.

22. exp aerobic exercise/ or exp anaerobic exercise/ or exp aquatic exercise/ or exp cardiopulmonary exercise test/ or exp dynamic exercise/ or exp exercise electrocardiography/ or exp exercise intensity/ or exp exercise physiology/ or exp exercise recovery/ or exp exercise test/ or exp exercise tolerance/ or exp leg exercise/ or exp muscle exercise/ or exp stretching exercise/ or exp treadmill exercise/ or exp arm exercise/
23. exp fitness/ or exp recreation/ or exp leisure/ or exp sports medicine/ or exp muscle strength/ or exp exercise/ or exp endurance/ or exp locomotion/ or exp mobilization/
24. exp sport/ or exp weight lifting/ or exp bicycle/ or exp running/ or exp swimming/ or exp walking/ or exp walking speed/ or exp walking difficulty/ or exp equipment/
25. exp isokinetic exercise/ or exp isometric exercise/ or exp isotonic exercise/ or exp kinesiotherapy/ or exp physiotherapy/ or exp muscle isometric contraction/ or exp muscle isotonic contraction/
26. (physical adj5 (exercise$ or conditioning or activit$ or fitness or therap$)).tw

27. (exercise adj5 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regime$)).tw
28. (fitness adj5 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regime$)).tw
29. ((training or conditioning) adj5 (intervention$ or protocol$ or program$ or activit$ or regime$)).tw
30. (sport$ or recreation$ or leisure or cycl$ or bicycl$ or treadmill$ or run$ or swim$ or walk$).tw
31. ((endurance or aerobic or cardio$) or adj5 (fitness or train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regime$)).tw
32. (muscle strengthening or progressive resist$).tw
33. ((weight or strength$ or resistance) adj5 (train$ or lift$ or exercise$)).tw
34. ((isometric or isotonic or eccentric or concentric) adj5 (contraction$ or exercise$)).tw
35. (muscle$ adj5 (conditioning or deconditioning or fitness)).tw
36. (idleness or immobility or inactivity).tw
37. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 21 and 37

CINAHL Search Strategy

The following search strategy will be added on to the strategy used in the review of the frequency and natural history of fatigue after stroke.

24. MH "Physical Fitness+") OR (MH "Fitness Centers") OR (MH "Balance Training, Physical") OR (MH "Recreation+") OR (MH "Exercise+") OR (MH "Abdominal Exercises") OR (MH "Aerobic Exercises+") OR (MH "Anaerobic Exercises") OR (MH "Aquatic Exercises") OR (MH "Arm Exercises") OR (MH "Back Exercises") OR (MH "Isokinetic Exercises") OR (MH "Isometric Exercises") OR (MH "Isotonic Exercises") OR (MH "Leisure Activities+") OR (MH "Physical Activity") OR (MH "Sports Medicine") OR (MH "Aeronautical Sports") OR (MH "Amateur Sports") OR (MH "Aquatic Sports+") OR (MH "Endurance Sports") OR (MH "Extreme Sports") OR (MH "Exercise Test+") OR (MH "Exercise Test, Cardiopulmonary") OR (MH "Exercise Test, Muscular+") OR (MH "Muscle Strength+") OR (MH "Muscle Strengthening+") OR (MH "Exercise Therapy: Ambulation (Iowa NIC)") OR (MH "Exercise Therapy: Balance (Iowa NIC)") OR (MH "Exercise Therapy: Joint Mobility (Iowa NIC)") OR (MH "Exercise Therapy: Muscle Control (Iowa NIC)") OR (MH "Exercise Tolerance+") OR (MH "Exertion+") OR (MH "Physical Endurance+") OR (MH "Physical Education and Training+") OR (MH "Physical Therapy+") OR (MH "Locomotion+") OR (MH "Movement+") OR (MH "Early Ambulation") OR (MH "Sports+") OR (MH "Weight Lifting") OR (MH "Cycling") OR (MH "Running+") OR (MH "Running, Distance") OR (MH "Swimming") OR (MH "Walking+") OR (MH "Ambulation: Walking (Iowa NOC)") OR (MH "Sports Equipment and Supplies+") OR (MH "Isometric Contraction") OR (MH "Isotonic Contraction+")

25. TX physical n5 exercise* or TX physical n5 conditioning or TX physical n5 activit* or TX physical n5 fitness or TX physical n5 therap*

26. TX exercise n5 train* or TX exercise n5 intervention* or TX exercise n5 protocol* or TX exercise n5 program* or TX exercise n5 therap* or TX exercise n5 activit* or TX exercise n5 regime

27. TX fitness n5 train* or TX fitness n5 intervention* or TX fitness n5 protocol* or TX fitness n5 program* or TX fitness n5 therap* or TX fitness n5 activit* or TX fitness n5 regime*

28. TX training n5 intervention* or TX training n5 protocol* or TX training n5 program* or TX training n5 activit* or TX training n5 regime*

29. TX conditioning n5 intervention* or TX conditioning n5 protocol* or TX conditioning n5 program* or TX conditioning n5 activit* or TX conditioning n5 regime*

30. TX sport* or TX recreation* or TX leisure or TX cycl* or TX bicycle* or TX treadmill* or TX run* or TX swim* or TX walk*

31. TX endurance n5 fitness or TX endurance n5 train* or TX endurance n5 intervention* or TX endurance n5 protocol* or TX endurance n5 program* or TX endurance n5 therap* or TX endurance n5 activit* or TX endurance n5 regime*

32. TX aerobic n5 fitness or TX aerobic n5 train* or TX aerobic n5 intervention* or TX aerobic n5 protocol* or TX aerobic n5 program* or TX aerobic n5 therap* or TX aerobic n5 activit* or TX aerobic n5 regime*

33. TX cardio* n5 fitness or TX cardio* n5 train* or TX cardio* n5 intervention* or TX cardio* n5 protocol* or TX cardio* n5 program* or TX cardio* n5 therap* or TX cardio* n5 activit* or TX cardio* n5 regime*

34. TX muscle strengthening or TX progressive resist*

35. TX weight n5 train* or TX weight n5 lift* or TX weight n5 exercise*

36. TX strength* n5 train* or TX strength* n5 lift* or TX strength* n5 exercise*

37. TX resistance n5 train* or TX resistance n5 lift* or TX resistance n5 exercise

38. TX isometric n5 contraction* or TX isometric n5 exercise*

39. TX isotonic n5 contraction* or TX isotonic n5 exercise*

40. TX eccentric n5 contraction* or TX eccentric n5 exercise*

41. TX concentric n5 contraction* or TX concentric n5 exercise

42. TX muscle* n5 conditioning or TX muscle* n5 deconditioning or TX muscle* n5 fitness

43. TX idleness or TX immobility or TX inactivity

44. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43

45. 23 and 44

Sport discus Search Strategy

1. (((((DE "CEREBROVASCULAR disease" OR DE "BRAIN -- Hemorrhage" OR DE "CEREBRAL embolism & thrombosis") OR (DE "CEREBRAL embolism & thrombosis")) OR (DE "ANEURYSMS")) OR (DE "BRAIN -- Hemorrhage")) OR (DE "HEMORRHAGE")) OR (DE "ARTERIAL occlusions" OR DE "ARTERIOSCLEROSIS" OR DE "EMBOLISM")

2. TX stroke or TX poststroke or TX post-stroke or TX cerebrovasc* or TX brain vasc* or TX cerebral vasc* or TX cva* or TX apoplex* or TX SAH

3. TX brain* n5 isch?emi* or TX brain* n5 infarct* or TX brain* n5 thrombo* or TX brain* n5 emboli* or TX brain* n5 occlus*

4. TX cerebr* n5 isch?emi* or TX cerebr* n5 infarct* or TX cerebr* n5 thrombo* or TX cerebr* n5 emboli* or TX cerebr* n5 occlus*

5. TX cerebell* n5 isch?emi* or TX cerebell* n5 infarct* or TX cerebell* n5 thrombo* or TX cerebell* n5 emboli* or TX cerebell* n5 occlus*

6. TX intracran* n5 isch?emi* or TX intracran* n5 infarct* or TX intracran* n5 thrombo* or TX intracran* n5 emboli* or TX intracran* n5 occlus*

7. TX intracerebral n5 isch?emi* or TX intracerebral n5 infarct* or TX intracerebral n5 thrombo* or TX intracerebral n5 emboli* or TX intracerebral n5 occlus*

8. TX brain* n5 haemorrhage* or TX brain* n5 hemorrhage* or TX brain* n5 haematoma* or TX brain* n5 hematoma* or TX brain* n5 bleed*

9. TX cerebr* n5 haemorrhage* or TX cerebr* n5 hemorrhage* or TX cerebr* n5 haematoma* or TX cerebr* n5 hematoma* or TX cerebr* n5 bleed*

10. TX cerebell* n5 haemorrhage* or TX cerebell* n5 hemorrhage* or TX cerebell* n5 haematoma* or TX cerebell* n5 hematoma* or TX cerebell* n5 bleed*

11. TX intracerebral n5 haemorrhage* or TX intracerebral n5 hemorrhage* or TX intracerebral n5 haematoma* or TX intracerebral n5 hematoma* or TX intracerebral n5 bleed*

12. TX intracranial n5 haemorrhage* or TX intracranial n5 hemorrhage* or TX intracranial n5 haematoma* or TX intracranial n5 hematoma* or TX intracranial n5 bleed*

13. subarachnoid n5 haemorrhage* or subarachnoid n5 hemorrhage* or subarachnoid n5 haematoma* or subarachnoid n5 hematoma* or subarachnoid n5 bleed*

14. (MH "Hemiplegia")

15. TX hemipleg* or TX hemipar* or TX paresis* or TX paretic*

16. (MH "Fatigue+") OR (MH "Fatigue (Saba CCC)") OR (MH "Fatigue Syndrome, Chronic") OR (MH "Muscle Fatigue") OR (MH "Fatigue (NANDA)")

17. (MH "Asthenia")

18. TX fatigue* or TX astheni* or TX neurastheni* or TX tired or TX tiredness or TX weary or TX weariness or TX exhaust* or TX lassitude or TX listlessness or TX letharg* or TX apath*

19. TX malaise

20. TX low n5 energy or TX lack n5 energy

21. S16 or S17 or S18 or S19 or S20

22. (MH "Physical Fitness+") OR (MH "Fitness Centers") OR (MH "Balance Training, Physical") OR (MH "Recreation+") OR (MH "Exercise+") OR (MH "Abdominal Exercises") OR (MH "Aerobic Exercises+") OR (MH "Anaerobic Exercises") OR (MH "Aquatic Exercises") OR (MH "Arm Exercises") OR (MH "Back Exercises") OR (MH "Isokinetic Exercises") OR (MH "Isometric Exercises") OR (MH "Isotonic Exercises") OR (MH "Leisure Activities+") OR (MH "Physical Activity") OR (MH "Sports Medicine") OR (MH "Aeronautical Sports") OR (MH "Amateur Sports") OR (MH "Aquatic Sports+") OR (MH "Endurance Sports") OR (MH "Extreme Sports") OR (MH "Exercise Test+") OR (MH "Exercise Test, Cardiopulmonary") OR (MH "Exercise Test, Muscular+") OR (MH "Muscle

Strength+") OR (MH "Muscle Strengthening+") OR (MH "Exercise Therapy: Ambulation (Iowa NIC)") OR (MH "Exercise Therapy: Balance (Iowa NIC)") OR (MH "Exercise Therapy: Joint Mobility (Iowa NIC)") OR (MH "Exercise Therapy: Muscle Control (Iowa NIC)") OR (MH "Exercise Tolerance+") OR (MH "Exertion+") OR (MH "Physical Endurance+") OR (MH "Physical Education and Training+") OR (MH "Physical Therapy+") OR (MH "Locomotion+") OR (MH "Movement+") OR (MH "Early Ambulation") OR (MH "Sports+") OR (MH "Weight Lifting") OR (MH "Cycling") OR (MH "Running+") OR (MH "Running, Distance") OR (MH "Swimming") OR (MH "Walking+") OR (MH "Ambulation: Walking (Iowa NOC)") OR (MH "Sports Equipment and Supplies+") OR (MH "Isometric Contraction") OR (MH "Isotonic Contraction+")

23. TX physical n5 exercise* or TX physical n5 conditioning or TX physical n5 activit* or TX physical n5 fitness or TX physical n5 therap*

24. TX exercise n5 train* or TX exercise n5 intervention* or TX exercise n5 protocol* or TX exercise n5 program* or TX exercise n5 therap* or TX exercise n5 activit* or TX exercise n5 regime*

25. TX fitness n5 train* or TX fitness n5 intervention* or TX fitness n5 protocol* or TX fitness n5 program* or TX fitness n5 therap* or TX fitness n5 activit* or TX fitness n5 regime*

26. TX training n5 intervention* or TX training n5 protocol* or TX training n5 program* or TX training n5 activit* or TX training n5 regime*

27. TX conditioning n5 intervention* or TX conditioning n5 protocol* or TX conditioning n5 program* or TX conditioning n5 activit* or TX conditioning n5 regime*

28. TX sport* or TX recreation* or TX leisure or TX cycl* or TX bicycle* or TX treadmill* or TX run* or TX swim* or TX walk*

29. TX endurance n5 fitness or TX endurance n5 train* or TX endurance n5 intervention* or TX endurance n5 protocol* or TX endurance n5 program* or TX endurance n5 therap* or TX endurance n5 activit* or TX endurance n5 regime*

30. TX aerobic n5 fitness or TX aerobic n5 train* or TX aerobic n5 intervention* or TX aerobic n5 protocol* or TX aerobic n5 program* or TX aerobic n5 therap* or TX aerobic n5 activit* or TX aerobic n5 regime*

31. TX cardio* n5 fitness or TX cardio* n5 train* or TX cardio* n5 intervention* or TX cardio* n5 protocol* or TX cardio* n5 program* or TX cardio* n5 therap* or TX cardio* n5 activit* or TX cardio* n5 regime*

32. TX muscle strengthening or TX progressive resist*

33. TX weight n5 train* or TX weight n5 lift* or TX weight n5 exercise*

34. TX strength* n5 train* or TX strength* n5 lift* or TX strength* n5 exercise*

35. TX resistance n5 train* or TX resistance n5 lift* or TX resistance n5 exercise*

36. TX isometric n5 contraction* or TX isometric n5 exercise*

37. TX isotonic n5 contraction* or TX isotonic n5 exercise*

38. TX eccentric n5 contraction* or TX eccentric n5 exercise*

39. TX concentric n5 contraction* or TX concentric n5 exercise*

40. TX muscle* n5 conditioning or TX muscle* n5 deconditioning or TX muscle* n5 fitness

41. TX idleness or TX immobility or TX inactivity

42. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41

43. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

44. (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15) and (21 and 43)

45. ((1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15) and (21 and 43)) and (42 and 44)

<u>PsycInfo Search Strategy</u>

The following search strategy will be added on to the strategy used in the review of the frequency and natural history of fatigue after stroke.

13. Physical fitness/ or recreation/ or recreation therapy/ or exercise/ or aerobic exercise/ or leisure time/ or daily activity/ or sports medicine/ or muscles/ or physical strength/ or walking/ or energy expenditure/ or heart rate/ or physical endurance/ or physical therapy/ or locomotion/ or activity level/ or sports/ or weightlifting/ or physical activity/ or running/ or swimming/ or health behaviour/ or athletic performance/ or muscle contractions/ or endurance/ or physical strength.mp
14. (physical adj5 (exercise$ or conditioning or activit$ or fitness or therap$)).tw
15. (exercise adj5 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regime$)).tw
16. (fitness adj5 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regime$)).tw
17. ((training or conditioning) adj5 (intervention$ or protocol$ or program$ or activit$ or regime$)).tw
18. (sport$ or recreation$ or leisure or cycl$ or bicycl$ or treadmill$ or run$ or swim$ or walk$)).tw
19. ((endurance or aerobic or cardio$) adj5 (fitness or train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regime$)).tw
20. (muscle strengthening or progressive resist$).tw
21. ((weight or strength$ or resistance) adj5 (train$ or lift$ or exercise$)).tw
22. ((isometric or isotonic or eccentric or concentric) adj5 (contraction$ or exercise$)).tw
23. (muscle$ adj5 (conditioning or deconditioning or fitness)).tw
24. (idleness or immobility or inactivity).tw
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 12 and 25

Appendix 8 - Data Extraction Form

This was completed for all potentially relevant papers.

Date of data extraction:

Identification features of the study
Record number (to uniquely identify study):
Author:

Article title:

Citation:
Type of publication (e.g. journal article, conference abstract):
Country of origin:
Source of funding:

Study Characteristics

Aims/ objectives of the study:

Study design:

Study inclusion and exclusion criteria:

Recruitment procedures used (consecutive patients, convenience sampling, retrospective recruitment):
Unit of allocation (e.g. participant, GP practice):
How is fatigue being measured?:

Has fatigue been separately assessed?
How is the study defining fatigue?
How is mood being measured?
How much time after stroke are measurements of mood being taken?

Number of times fatigue has been separately assessed:
Time between assessments of fatigue (length of follow up):

Participant Characteristics

How have they defined the study population. (e.g. stroke patients, people over 65, people with depression):

Total number of participants at recruited to study:
Total number of participants at end of study:
Number of participants who died before end of study:
Number of participants who dropped out or were lost to follow-up before end of study:
Characteristics of those who dropped out:

Age:
Age limits used in the study:

Gender:
First or recurrent stroke:
How exercise/ activity before stroke is measured:

Depression before stroke (if mentioned):
Ethnicity:
Socio-economic status:
Type of stroke:
Stroke subtype:
Stroke severity measure and score:
Co-morbidities:

Type of activity, intervention (if relevant) and setting

Description of the setting in which the physical activity is taking place. (eg treadmill in a lab setting or in the participant's own home etc):

Description of the type of physical activity the participants in the study are undertaking. E.g. normal leisure activities, walking, bowling or structured fitness classes at a community centre.

<u>Outcome data/ results</u>

Were participants put into subgroups (i.e. age groups, stroke subtype groups).
What were the groups (i.e. under 65, 65 – 80, 80+).

Can fatigue data for stroke patients be extracted separately from other types of patients?:
Has fatigue and/or depression data been reported?
Measurement tools, techniques or methods used for measuring physical activity, fitness or muscle strength:

Measurement tools or methods used for measuring fatigue and/ or depression

Unit of measurement (miles per day, hours per day, Newtons, Watts):

Length of follow-up:
Number and/or times of follow-up:
For each subgroup (if appropriate)
Number of participants recruited:

Number of participants included in analysis:
Number of withdrawals, exclusions, lost to follow up:

Summary outcome data (extract for each subgroup)

Dichotomous	Number with fatigue:
	Number without fatigue:
Continuous	Mean and SD of fatigue scale (whichever is used).
	Mean and SD of physical activity measure(s)
	Data presented as correlations and/or associations
Categorical	Categories of physical activity participants take part in:

Methods of statistical analysis including variables adjusted for:

Which variables were compared or correlated:

Has there been any attempt to compare or associate fatigue data with physical activity data.

Results of study analysis (extract for each patient sub-group)

Dichotomous	p-value, confidence intervals
Continuous	mean difference, confidence intervals, Pearson's or Spearman's r value & p-value

Details of any additional relevant outcomes reported:

Amount of missing data and which methods (if any) were used to deal with it:

Appendix 9 - Published paper "Clinically significant fatigue after stroke: A longitudinal cohort study."

The full reference for this paper is: Duncan F., Greig C., Lewis S., Dennis M., MacLullich A., Sharpe M. and Mead G. (2014) Clinically significant fatigue after stroke: A longitudinal cohort study. *Journal of Psychosomatic Research*. 77(5), pp 368-373.

Abstract (250words)

Objective Fatigue is often distressing for stroke survivors. The time course of clinically significant fatigue in the first year after stroke is uncertain.

We aimed to determine the frequency, severity and time course of clinically significant fatigue in the first 12 months after stroke onset.

Methods We recruited patients with a recent acute stroke. At about one month, six months and 12 months, we performed a structured interview to identify clinically significant fatigue (case definition), and assessed fatigue severity (Fatigue Assessment Scale (FAS)).

Results Of 157 patients who initially consented, 136 attended at least one assessment. At one month, 43/132 (33%) had clinically significant fatigue. Eighty-six attended all three assessments, of whom clinically significant fatigue was present in 24 (28%) at one month, 20 (23%) at six months and 18 (21%) at 12 months; their median (IQR) FAS scores were 23 (18 to 29), 21 (17 to 25) and 22.5 (17 to 28) at one, six and 12 months respectively.

Of 101 patients who attended at least the one and six month assessments, fatigue status did not change in 65 (64%), with 9 (9%) fatigued throughout and 56 (55%) non-fatigued throughout; 15 (15%) became non-fatigued, 9 (9%) became fatigued, and in 12 (12%) fatigue status fluctuated across three assessments.

Conclusion Clinically significant fatigue affected a third of patients one month after stroke. About two thirds of these patients had become non-fatigued by six months, most of whom remained non-fatigued at 12 months. Fatigue persists in a third at 12 months.

Introduction

Fatigue is a common problem after stroke [1] for which there is currently no effective treatment [2]. Understanding the time course of fatigue after stroke is important, so that healthcare professionals can counsel patients about whether it is likely to improve over time. If fatigue persists in a substantial proportion of patients, this would justify the development of interventions. There is one published systematic review of longitudinal cohort studies of post-stroke fatigue (9 studies reporting on 959 patients)[3] and one further longitudinal study published since that review[4]. These studies determined the presence or absence of fatigue using either a cut-off score on one of several different scales, or a single question. Two studies included in the review used the fatigue severity scale, but used different 'cut-off' points to define fatigue, and it is unclear whether these cut-offs represent fatigue that is clinically important to patients. The review concluded that the proportion of patients with fatigue early after stroke ranged from 35% to 92% and that fatigue remained common in the longer term. The proportion of patients with fatigue declined over time in seven (n=764) of the studies and increased in two (n=195).[3] However, methods used to define fatigue in previous studies do not tell us about fatigue that is perceived as problematic by patients. Previous cross-sectional studies of post-stroke fatigue have also used cut-off points on fatigue scales, and the cut-off points have generally been determined using data from other patient populations[5-7]. These cross sectional studies cannot tell us whether fatigue improves over time.

Fatigue is an experience common to all, so arguably the distinction between 'normal' and 'pathological' fatigue is unavoidably arbitrary. Nevertheless, the concept of physiological' (or normal) fatigue (a state of general tiredness which develops acutely after overexertion and improves after rest) and 'pathological fatigue' ('constant weariness unrelated to previous exertion levels and not usually ameliorated by rest')[8] has been developed in the stroke literature. In neurological diseases including stroke, 'pathological fatigue' is generally considered more prominent than 'physiological' fatigue. [9]. Stroke survivors report that the fatigue experienced after stroke is unlike 'normal' fatigue they had experienced prior to stroke[10], that it starts shortly after the stroke and that they believe that is a consequence of the stroke [11]. Thus, the concept of 'clinically significant fatigue' has face validity. In order to identify 'clinically significant post-stroke fatigue' in practice, we developed a case definition and associated structured interview, based on the definition of post-stroke fatigue proposed by other authors, and qualitative interviews with stroke survivors who had fatigue. We subsequently showed that the case definition was valid and reliable [12]. The case definition requires fatigue to be present for >50% of waking hours on most days, and crucially, the fatigue needs to interfere with activities of daily living[12]. The definition of 'clinically significant fatigue' can be refined by evaluating the severity of fatigue [13]. We have previously shown that the fatigue assessment scale (FAS) [14] is valid and reliable after stroke[13]. Thus, our approach to assessing post-stroke fatigue in research studies is to assess whether the case definition is fulfilled, and also fatigue severity using the FAS.

Although there are several published longitudinal cohort studies which have reported the course of fatigue after stroke [3, 4] no previous studies have used a case definition approach to identify clinically significant post-stroke fatigue over the first year.

The aim of this longitudinal cohort study was to determine the time course of clinically significant fatigue over the first year after stroke, and changes in its severity. [12]

Methods

Design

A longitudinal cohort study with follow up over 12 months.

Ethical approval

Approval from Lothian Research Ethics Committee was obtained and all participants gave written informed consent

Recruitment

From 1st September 2009 to 30th June 2011, we recruited participants who had been admitted to the Western General Hospital and Royal Infirmary of Edinburgh or seen in an outpatient clinic with a new acute haemorrhagic or ischaemic stroke. Patients had to have postcodes in South Edinburgh or East Lothian to ensure the patients sampled related to a defined population. They could be recruited at any time within the first month of stroke, though in practice most consented a few days after admission to an acute stroke unit.

Patients on the participating acute stroke units were approached face-to-face by the study researcher. Those who had been out-patients were given an information sheet by the clinic doctor and, if they were interested in participating, their details were sent to the study researcher who then contacted them by telephone. Exclusion criteria were: subarachnoid haemorrhage (unless secondary to an intraparenchymal haemorrhage); severe dysphasia or severe cognitive impairment that would prevent completion of the questionnaires; medically unstable and/ or considered too unwell by the clinical team to participate.

Baseline measures

Stroke subtype (Oxfordshire Community Stroke Project Classification (OCSP) and patient characteristics were obtained from medical notes. At recruitment the Mini-mental state examination (MMSE) and National Institute of Health Stroke Scale (NIHSS) were administered.

The National Institutes of Health Stroke Scale (NIHSS) is a 15 item systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit in the early stages after stroke. [16] The maximum possible total score is 42 (representing the most severe neurological deficit), and the minimum possible score is 0 (presenting the least severe neurological deficit).

In order to determine whether fatigue before stroke was likely to influence fatigue after stroke, participants were asked 'Did you have a problem with fatigue before your stroke' (requiring a "yes" or "no" response). Participants were invited to attend follow-up assessments at one month, six months and 12 months after stroke onset.

Follow-up measures

Case definition fulfilment

At each of the follow-up assessments, a structured interview was administered which included seven 'probe' questions to determine whether or not a participant fulfilled our case definition for clinically significant fatigue[3]. Case definition fulfilment required that participants had experienced fatigue, a lack of energy or an increased need to rest, every day or nearly every day for more than 50% of the day, for at least a two week period in the past month; and this fatigue had affected their ability to take part in everyday activities or have been perceived to have been a problem.

The Fatigue Assessment Scale (FAS)

The participant also completed the FAS, a 10 item self-report scale, with each item scored from one to five (1 = never, 2 = sometimes, 3 = regularly, 4 = often, 5 = always). Total scores range from 10 to 50, with a higher score indicating more fatigue. The FAS has been tested for validity and reliability in stroke [13]. A change of four points or more has previously been considered to represent a clinically relevant change in fatigue status [15] in patients with sarcoidosis; and so in this paper we also reported the change in 4 points or more in the FAS.

Analysis

We determined the proportion with clinically significant fatigue and the median (interquartile range) of FAS at each time point using all available data and also for only those patients who attended all three assessments. We also reported changes in fatigue status over time, both according to the case definition and to a change of at least four points in FAS.

Results

Recruitment

We approached a total of 382 eligible patients, of whom 157 agreed to take part. The median time from stroke onset to consent was 5 days (IQR 3-10). Our ethical approval did not allow us to systematically record why patients did not wish to take part; however our impression was that patients who declined were uncertain about availability for follow-up, disliked questionnaires or felt that they already had too much to think about at the time of the stroke.

Of the 157 patients who consented, 21 (13%) did not attend any assessment visits and were excluded from further analyses.

Table 1 compares the demographics of the 86 patients who attended all three assessments with the 44 patients who dropped out or died after one or six months. There were no significant differences between the two groups.

Table 1 about here

Attendance at assessments

The assessments at one, six and 12 months after stroke onset were attended by 132 (97%), 105 (77%) and 91 (67%) participants respectively. 86 (63%) participants attended all 3 assessments, 29 (21%)

dropped out after the one month assessment (including nine who had died), 15 (11%) dropped out after the six month assessment (including three who had died), 3 (2%) attended only the six and 12-month assessments, one (1%) attended only the 6-month assessment and two (2%) attended only the one and 12- month assessments. (figure)

Sixteen of the 43 (37%) subjects with fatigue at one month did not attend at six months compared to 15 of the 89 (17%) of those without fatigue at one month (p=0.015, Fisher's Exact Test).

<u>Frequency and severity of fatigue after stroke: entire cohort</u>

Clinically significant fatigue was present in 43/132 (33%) of those who attended the one-month visit, 23/105 (22%) of those who attended the six-month visit and 18/91 (20%) of those who attended the 12-month visit.

The median (IQR) FAS score was 23 (18 to 29) at one month, 21 (17 to 25.5) at six months and 22 (17 to 28) at 12 months.

<u>Frequency and patterns of fatigue after stroke in patients who attended all three assessments</u>

Of the 86 patients who attended all three assessments, clinically significant fatigue was present in 24 (28%) at one month, 20 (23%) at six months and 18 (21%) at 12 months. Median (IQR) FAS score was 23 (18 to 29) at one month, 21 (17 to 25) at six months and 22.5 (17 to 28) at 12 months (significant difference between one and six months, p=0.025; p=0.19 for between six months and 12 months (Wilcoxon Signed Rank tests)).

<u>Influence of previous stroke on proportion with fatigue:</u>

We explored the influence of previous stroke on the proportion with fatigue: 21 (24%) of these 86 patients had had a previous stroke; six (29%) of these had a positive case definition at one month, 7 (33%) at six months and 5 (24%) at 12 months.

Relationship between case definition and FAS

At each time point, those who fulfilled the case definition for fatigue had significantly higher median FAS scores than those who did not: 29 (IQR 24-33, n=43) compared to 21 (16.5-25, n=89) at one month, 28 (22-38, n=23) compared to 19 (16-24, n=82) at six months, 29 (24.75-38.25, n=18) compared to 20 (15-25, n=73) at 12 months. All comparisons were significant at $p<0.001$ (Mann-Whitney U tests).

Changes in fatigue over time: case definition

Table 2 shows the observed patterns of fatigue across 12 months after stroke, according to the case definition. Of the 86 patients attending all three assessments, fatigue status did not change in 52 (60%), with 7 (8%) fatigued and 45 (52%) non-fatigued throughout; 14 (16%) became non-fatigued by six or 12 months; 8 (9%) became fatigued by six or 12 months; fatigue status fluctuated over the three assessments during the 12 month period in the remaining 12 (14%) patients. Of the 15 patients attending the one and six month assessments only, fatigue status did not change in 13 (87%), with 2 (13%) being fatigued and 11 (73%) non-fatigued at both assessments. One (7%) became non-fatigued and one (7%) became fatigued between one and six months.

Of 101 patients who attended at least the one and six month assessments, fatigue status did not change in 65 (64%), with 9 (9%) fatigued throughout and 56 (55%) non-fatigued throughout; 15 (15%) became non-fatigued, 9 (9%) became fatigued, and in 12 (12%) fatigue status fluctuated across the three assessments.

Table 2 about here

Changes in fatigue over time: FAS

Table 3 demonstrates the pattern of fatigue after stroke across 12 months according to the FAS. Between one and six months, changes in fatigue scores of four points or more showed an increase (more severe fatigue) in 24/101 (24%) patients, a decrease in 35/101 (35%) patients and in the remaining 42/101 (42%) patients, the change was less than four points. Between six and 12 months, changes in fatigue score of four points or more showed an increase in 25/86 (29%) patients, a decrease in 17/86 (20%) patients and in the remaining 44 patients (51%), the change was less than four points.

The median (IQR) change between one and six months in those whose scores increased was 6.5 (4.25 to 10.5) and in those whose scores decreased it was -7 (-11 to -5).

Table 3 about here

Relationship between patient-reported pre-stroke fatigue and post-stroke fatigue

Those with fatigue before stroke had significantly higher FAS at six and 12 months after stroke than those without fatigue before stroke. A significantly higher proportion of those with fatigue before stroke had a positive case definition at six months after stroke (Table 4).

Table 4 about here

Discussion

This is the first longitudinal cohort to use a case definition and structured interview to identify clinically significant post-stroke fatigue. Using this definition, about one third of patients had clinically significant fatigue one month after stroke. This is lower than identified in previous studies (35% to 92%), possibly because the case definition identified only fatigue that lasted for more than half the day and which was considered as a problem to patients, whereas previous studies used a single question or a cut-off point on a scale and so may have identified patients with milder fatigue.

About two thirds of the patients with fatigue at 1 month had become non-fatigued by six months and most remained non-fatigued at 12 months, but one third of the patients with fatigue at one month still had fatigue at 12 months. We also found that there was a statistically significant fall in fatigue severity over the first six months. However, fatigue may develop in a small proportion of patients over the first year (Table 2). Our findings are consistent with three other longitudinal studies which examined the course of fatigue after stroke (using a fatigue scale) for individual patients [4, 17 18 19]. Taken together, the data from FAS and case definition show that fatigue status and severity can change over time. There were insufficient data to determine the factors associated with a change from being fatigued to not being fatigued according to the case definition. This requires exploration in future studies.

The strengths of this study are that we used two instruments for assessing fatigue; the fatigue case definition (to identify clinically significant fatigue) and the FAS (for fatigue severity) which have both been validated and tested for reliability and feasibility in stroke patients [13] [12]. We also used a clinically meaningful case definition.

The study also had some weaknesses: not all eligible patients agreed to participate, so we cannot be certain how generalizable our results are. Ethical approval did not allow us to systematically record reasons why people refused to participate or why patients who had initially consented decided not to continue in the study. Fatigue at one month was associated with non-attendance at six months. We took into account the possibility of non-response bias by reporting the time course in the 86 patients who had completed all three assessments. The findings were similar, though the frequency of fatigue at one month was slightly lower at 28% compared with 33% in all of the patients attending at one month. We would have obtained a more precise measure of fatigue frequency had the study been larger, but we were limited by available resources.

Almost half answered 'yes' to the question 'Did you have a problem with fatigue before your stroke?' There is no validated method to determine pre-stroke fatigue retrospectively, and so we cannot be certain about the validity of this measure. The fatigue that patients reported may have been normal 'physiological' fatigue[20], whereas stroke survivors themselves often report that the fatigue experienced prior to a stroke tends to be different in quality from post-stroke fatigue. [21]

This study has found that clinically significant fatigue is sufficiently common that clinicians involved in the management of stroke survivors should ask about fatigue at follow-up visits. They should inform stroke survivors that fatigue may resolve spontaneously over time. In addition, there are implications for future research. First, studies are needed to determine which factors are associated with persisting fatigue and which factors are associated with spontaneous resolution of fatigue. As mood and anxiety scores have been found to be associated with fatigue at a single time point [7], future longitudinal studies should explore whether changes in mood are associated with changes in fatigue. Second, there is a need for studies of factors that facilitate adaptation to fatigue; these may include self-efficacy, locus of control, as well as rehabilitation or social support received. Third, our data suggest that clinically significant fatigue is sufficiently common and persistent to justify the development of an intervention, the evaluation of which should control for spontaneous recovery of fatigue.

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Table 1: Characteristics at recruitment of participants who attended all visits and those who dropped out or died after 1 or 6 months

Characteristics at recruitment	**Participants who completed all 3 assessments (n=86)**	**Participants who dropped out or died after 1 or 6 months (n=44)**
Median age, years (IQR)	71.8 (63.5 to 79.8)	71.9 (61.2 to 79.5)
Male (%)	53 (62)	31 (71)
First ever stroke (%)	65 (76)	36 (81)
Inpatient (%)	78 (91)	42 (96)
Ischaemic stroke (%)	80 (93)	41 (93)
Left hemisphere (%)	38 (51) n=75	13 (32) n=41
Oxford Community Stroke Project class:		
TACS (%)	3 (4)	2 (4)
PACS (%)	34 (39)	18 (41)
LACS (%)	26 (30)	14 (32)
POCS (%)	23 (27)	10 (23)
Answered ‘yes’ to question ‘Did you have a problem with fatigue before your stroke?’ (%)	41 (48)	14 (32)
History of diabetes (%)	15 (17)	7 (16)
History of hypertension (%)	44 (51)	24 (55)
Median MMSE (IQR)	28 (25 to 29) n=76	26 (25 to 28) n=40
Median NIHSS (IQR)	2 (1 to 3.75) n=84	3 (2 to 4) n=44
Mean (SD) Systolic BP at admission	148.2 (26.5) n=82	146.6 (28.1) n=41
Mean (SD) Diastolic BP at admission	78.9 (14.2) n=82	81.6 (15.6) n=41

TACS - total anterior circulation syndrome, PACS - partial anterior circulation syndrome, LACS - lacunar syndrome, POCS - posterior circulation syndrome
T-test, Mann-Whitney U test, Chi-square test or Fisher’s Exact test

Table 2 Profile of case definition for fatigue across assessments

	Pattern of Case definition		Assessment			n (%)
			1 month	**6 months**	**12 months**	
Attended three assessments (n=86)	No change	Remained fatigued	Y*	Y	Y	7 (8)
		Remained non-fatigued	N*	N	N	45 (52)
	Became non-fatigued		Y	Y	N	1 (1)
			Y	N	N	13 (15)
	Became fatigued		N	N	Y	5 (6)
			N	Y	Y	3 (4)
	Fatigue fluctuated		Y	N	Y	3 (4)
			N	Y	N	9 (10)
Attended two assessments (n=20)	No change	Remained fatigued	Y	Y		2 (10)
		Remained non-fatigued	N	N		11 (55)
				N	N	3 (15)
			N		N	1 (5)
	Became non-fatigued		Y	N		1 (5)
			Y		N	1 (5)
	Became fatigued		N	Y		1 (5)
Attended one assessment (n=30)			Y			15 (50)
			N			14 (47)
				N		1 (3)
Total						**136**

* Y Positive case definition for fatigue
* N Negative case definition for fatigue

Table 3 Change in Fatigue Assessment Scale (FAS) scores of four points or more across assessments

Change* in FAS score between 1 & 6 months		**Subsequent change* in FAS score between 6 & 12 months**	
n (%) of participants	**Median change (IQR)**	**n (%)**	**Median Change (IQR)**
Increase (more fatigue) 24 (24)	6.5 (4.25 to 10.5)	Increase 1 (6)	(value 4)#
		No change 6 (35)	0 (-2.25 to 2.25)
		Decrease 10 (59)	-8 (-15 to -6.75)
		(7 did not attend 12-month assessment)	
No change 42 (42)	-0.5 (-2 to 1)	Increase 12 (32)	6 (5 to 7)
		No change 22 (60)	0 (-2 to 2.25)
		Decrease 3 (8)	-6 (values -7, -6, -5)#
		(5 did not attend 12-month assessment)	
Decrease (less fatigue) 35 (35)	-7 (-11 to -5)	Increase 12 (37)	8.5 (6.25 to 10.75)
		No change 16 (50)	1 (-0.75 to 2)
		Decrease 4 (13)	-5.5 (-6 to -4.25)
		(3 did not attend 12-month assessment)	
Total 101 (35 did not attend 1- or 6-month assessment)	-1 (-5.5 to 3)	**Total** 86 (15 did not attend 12-month assessment)	1 (-3 to 5)

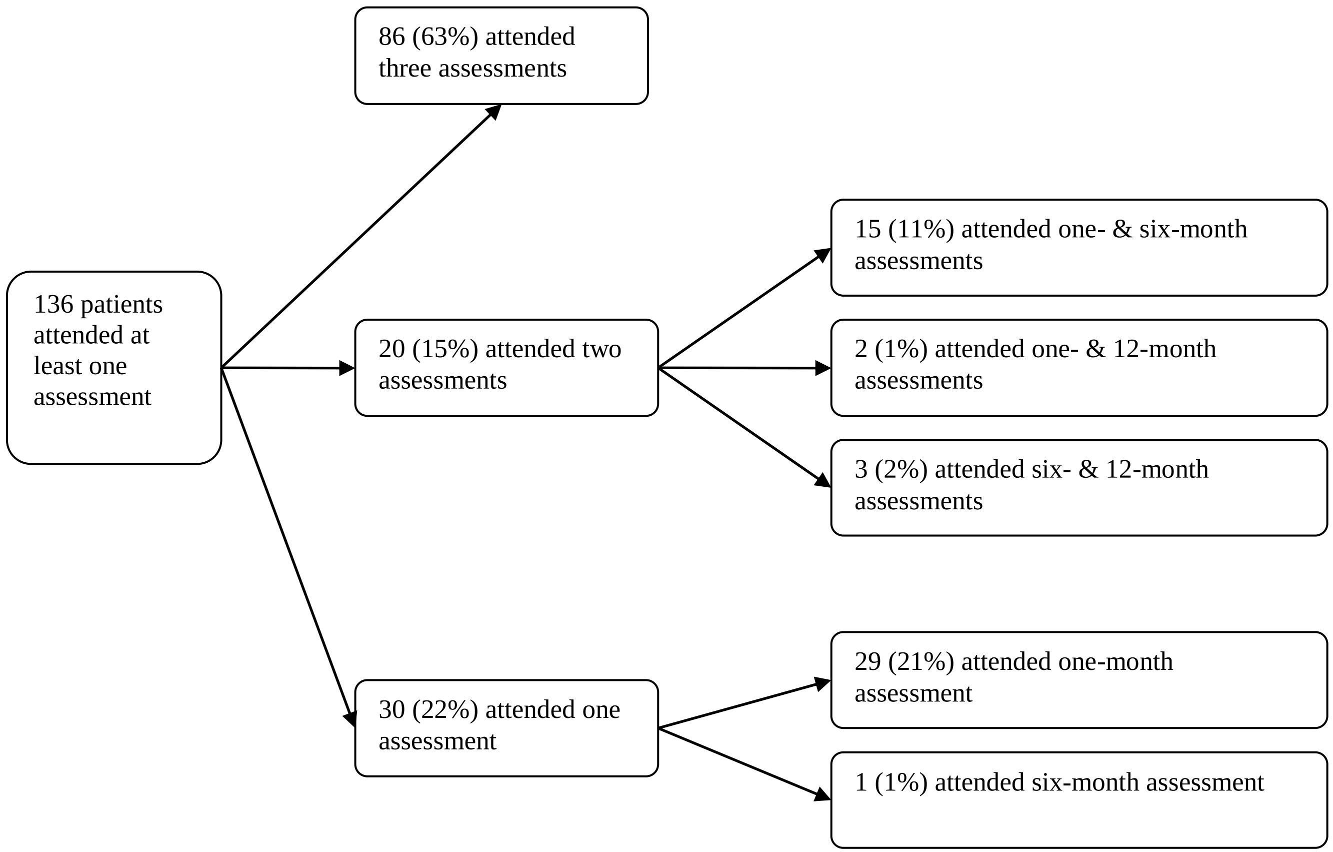
* Increase - increase of 4 points or more
No change - change of less than 4 points
Decrease - decrease of 4 points or more

Too few patients to report median and /or IQR. Actual values are given

Table 4 FAS & Case definition in relation to fatigue before stroke

	Fatigue before stroke?		Mann-Whitney Test (p)
	Yes	No	
FAS at 1 month (median (IQR))	24 (18 to 29.75) n=56	23 (17.25 to 28) n=76	0.67
FAS at 6 months (median (IQR))	22 (19 to 26) n=47	19 (17 to 24.25) n=58	0.032
FAS at 12 months (median (IQR))	24 (19 to 30) n=43	21 (15 to 25.75) n=48	0.031

		Fatigue before stroke?		Fisher's Exact Test (p)
		Yes	No	
Case definition at 1 month	Yes (43)	19 (44%)	24 (56%)	0.85
	No (89)	37 (42%)	52 (58%)	
Case definition at 6 months	Yes (23)	15 (65%)	8 (35%)	0.033
	No (82)	32 (39%)	50 (61%)	
Case definition at 12 months	Yes (18)	11 (61%)	7 (39%)	0.20
	No (73)	32 (44%)	41 (56%)	


136 patients attended at least one assessment
86 (63%) attended three assessments
20 (15%) attended two assessments
30 (22%) attended one assessment
15 (11%) attended one- & six-month assessments
2 (1%) attended one- & 12-month assessments
3 (2%) attended six- & 12-month assessments
29 (21%) attended one-month assessment
1 (1%) attended six-month assessment

Appendix 10 - Patient Information Sheet

Edinburgh Fatigue After Stroke Study

Patient Information Sheet

Contact details of researchers

Fiona Duncan – Research Assistant
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Dr Gillian Mead – Principal Investigator and consultant of stroke medicine
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Summary of Study

- You are being invited to take part in a research study
- Take time to decide whether or not you wish to take part

Purpose of Study

We want to find out about tiredness (fatigue) after stroke.

Specifically we want to find out:
- How common it is?
- How long it lasts for?
- What causes it?
- Is it related to being less physically active?

What will happen if you take part?

If you agree to take part the researcher will see you three times:
- 1 month after your stroke
- 6 months after your stroke
- 12 months after your stroke

You will be invited to come into the Clinical Research Facility which is on the ground floor of the Royal Infirmary of Edinburgh. If you prefer the researcher will visit you at home.

What will happen at each assessment?

- A short interview about tiredness
- Questionnaires
- Physical activity monitoring
- A blood sample will be taken for those who attend Clinical Research Facility

If you come to the Clinical Research Facility we will send and pay for a taxi to take you there and back.

Please take the time to read the attached information sheet for further details about the study.

Patient information sheet. Version 3. August 2010

1. Study Title
A longitudinal study of fatigue after stroke and its relationship with physical activity

2. Invitation

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.
- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

3. What is the purpose of this study?

Fatigue (tiredness) is common in patients who have had a stroke, but very little research has been done to find out just how common it is, how long it lasts, or what causes it. We want to find out how common fatigue is at 1 month, 6 months and 12 months after stroke. We also want to find out whether fatigue is related to being less physically active. This new information will help us to develop new treatments for fatigue.

4. Why have I been chosen to take part?

You have been chosen to take part because you recently had a stroke. This study will recruit 170 patients who have had a stroke from stroke wards and stroke clinics in Edinburgh over a 17 month period.

5. Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time or a decision not to take part will not affect the care you receive.

6. What will happen to me if I take part?

You will be approached by the researcher soon after your stroke. You will then be assessed 1 month, 6 months and 12 months after your stroke. These assessments will be in addition to the standard care you will receive. Your care will not be affected by participation in the study.

Initial visit by researcher
The researcher will visit you on your ward (or if you have been discharged, the researcher will arrange a suitable place to meet you). Information about your stroke will be collected from your medical notes, and you will be asked some questions about your stroke.


The Researcher – Fiona Duncan

Assessment at 1 month
The research assistant will meet with you again, in hospital or in our Clinical Research Facility at the Royal Infirmary, Edinburgh. If you have been discharged from hospital and would prefer to be seen at home, we can arrange this, though our tests of physical fitness cannot generally be performed in patients' homes.
There are four parts to this assessment:
a) we will interview you,
b) we will test your physical fitness. This includes muscle strength, power and, if you are able to walk, the distance you can walk.
c) we will take a blood sample and
d) we will attach a small physical activity monitor for you to wear at home.

a) Interview: This interview will find out whether you feel tired. We will also ask you some questions to find out if you have any problems with your mood, your sleep, what you think about your stroke, your quality of life, and how your stroke has affected your ability to do everyday things.

b) Tests of physical fitness. Your leg muscle strength and power will be measured by simple pushing movements which you will be asked to hold for a few seconds. This series of tests will take about 20 minutes so you may feel a little tired afterwards but the tests should not cause any pain or discomfort.

If you are able to walk after your stroke, we will ask you to walk for 6 minutes, or if you can't walk for this long, we will ask you to walk as far as you can. We will make every effort to minimise the risk of a stumble or fall. We have extensive experience of conducting muscle function and walking tests on patients with stroke.

c) Blood samples
We will also ask your permission to take a small sample of blood (10ml or about two teaspoons). This will be stored for future analysis of potential blood 'markers' of fatigue.

These assessments will take about 2 hours to perform.

d) Physical activity monitoring
Just before you go home after your first visit we will attach a small physical activity monitor to your thigh with sticky pads and ask you to wear it for 7 days. We will ask you to remove some of your clothing for a few minutes so that we can attach the monitor. The monitors are very small (1.5 x 2.5 inches) and lightweight (less than 1oz in weight). You may have a bath or a shower during this time (although if you wish to bathe we would ask you to remove the monitor while you are bathing).

We will ask you to post back your monitor after one week in the stamped-addressed envelope which we will provide.

Physical Activity Monitor

<u>Assessments at 6 months and 12 months</u>

We will invite you to participate in the same assessments at 6 months and 12 months after your stroke.

We will pay your travelling expenses for all the assessments you undergo.

<u>Brain Imaging</u>

You will have had a scan taken of your brain (usually a computed tomography scan and sometimes an additional magnetic resonance scan) as part of your usual medical care. We would like to ask for your permission to have your brain scan read by a consultant neuroradiologist.

<u>Data Linkage</u>

The National Health Service Central Register (NHSCR) contains basic details of everyone born in Scotland, plus anyone else who is (or has been) on the list of a general medical practitioner in Scotland. We would like to ask for your permission to use information held by the NHS and records maintained by the National Health Service Central Register for Scotland to keep in touch with you and follow up your health status in the longer term.

Salivary Cortisol

We will also ask you to collect a sample of your own saliva. This involves chewing on a small cotton swab and placing it in a sterile plastic container. This will be analysed to see if levels of saliva cortisol can be linked to fatigue and will be used for no other purpose.

7. What do I have to do?

There are no lifestyle restrictions.

8. What are the possible benefits of taking part?

Some patients find it helpful to talk to someone about their symptoms after a stroke. The information we get from the study may help us to treat patients with stroke better in the future.

9. What are the possible disadvantages and risks of taking part?

Apart from the possible inconvenience of the researcher taking up some of your time, we do not envisage any particular risks in your taking part.

The tests of physical activity and muscle function may make you feel a little tired and possibly a little stiff afterwards, and the walking test may make you feel a little puffed out.

After a blood test, very occasionally there may be a small amount of bruising at the site of the test, but the risk of this will be minimized by ensuring that the researcher taking the blood has received appropriate training.

10. What happens when the research study stops?

We will ask your permission to store your blood samples in the Clinical Research Facility, Royal Infirmary so that we can consider them for use in future research studies that we may carry out. Any future use of the samples would not identify you by name, and would require the approval of a Research Ethics Committee for that project.

For further information, please see Part 2 of this information sheet.

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

For further information, please contact Dr Gillian Mead, Consultant Stroke Physician, who is leading the study. Her phone number is 0131 242 6481.

If you have any concerns about the study, please contact Dr Mead in the first instance.

Appendix 11 - Participant Consent Form

GERIATRIC MEDICINE
Clinical and Surgical Sciences

SCHOOL *of* CLINICAL SCIENCES
and COMMUNITY HEALTH

The University of Edinburgh
Room S1642
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh EH16 4SA

Secretaries: Mrs M Harding
Mrs L Eggins

Telephone 0044 (0)131 242 6481
Fax 0044 (0)131 242 6370

www.geriatric.med.ed.ac.uk

Centre Number::
Study Number:
Patient Identification Number for this trial:

CONSENT FORM
Version 4 May 2010

Title of Project: A longitudinal study of fatigue after stroke physical activity

Name of Researcher: Dr Gillian Mead

Please initial box

1. I confirm that I have read and understand the information sheet dated ....(version ....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from University of Edinburgh, from regulatory authorities or from

4. I agree to my GP and my Chest, Heart and Stroke Nurse being informed of my participation in the study. ☐

5. I agree to have my brain scan (taken as part of my usual medical care) read by a consultant neuroradiologist**.** ☐

6. I understand that information held by the NHS and records maintained by the National Health Service Central Register for Scotland may be used to keep in touch with me and follow up my health status ☐

7. I agree that my blood and saliva may be stored for future analysis ☐

8. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix 12 - Number of answers that were missed for each self report questionnaire.

Epworth Sleepiness Scale – one month

Participant identification Number	Number of answers missed
007	1
015	1
017	2
047	2
073	1
088	1
094	2
110	2
114	1
135	1
150	3

Epworth Sleepiness Scale – six months

Participant identification Number	Number of answers missed
047	3
073	1
081	1
088	1
105	1
133	1

Epworth Sleepiness Scale – 12 months

Participant identification Number	Number of answers missed
026	1
077	1
081	1

HADS anxiety scale – One month

Participant identification Number	Number of answers missing
007	1
040	1
065	1
073	1

HADS depression scale – one month

Participant identification Number	Number of answers missing
007	2
040	1
088	1

HADS anxiety scale – six months

Participant identification Number	Number of answers missing
005	1
096	3
131	3

HADS depression scale – six months

Participant identification Number	Number of answers missing
026	2
096	2
131	1

Hospital Anxiety and Depression Scale – 12 months

Participant identification Number	Number of answers missing
027	1
086	1
131	1

Fatigue Assessment Scale – One month

Participant identification Number	Number of answers missing
007	1
016	1
062	1
090	1
103	1
116	1

Fatigue Assessment Scale – six month

Participant identification Number	Number of answers missing
005	2
096	4
116	1
131	5

Fatigue Assessment Scale – 12 months

Participant identification Number	Number of answers missing
077	1
096	1
106	1
131	1
141	1

Appendix 13 – Service user group comments and action taken.

Service user group member's comments	Action that was taken
It is very important to involve carers as much as possible in the research study. The carer could motivate the patient to continue to take part in the study	At recruitment the participant was encouraged to tell their carer that they have agreed to take part in a research study and will be told that carers are welcome to attend the follow-up assessments.
The Chest, Heart and Stroke Nurse is very influential and visits participant regularly after stroke.	The Chest, Heart and Stroke nurse was informed by letter when a patient is recruited to the study.
It is very important to treat participants as individuals and to reassure them that they are normal at each part of the research study.	These comments were taken into account when participants were being recruited and during follow-up assessments.
Potential participants would be more likely to take part if they felt they were helping someone else.	The benefits for others were emphasised to participants at recruitment and during assessments
Dr Mead's title, "Reader in Geriatric Medicine" may put off younger participants from wanting to take part and older participants may be offended by the word "Geriatric".	Title changed to "Consultant Physician"
The information sheet was considered to be too long, complicated and the writing style was not as clear as it could be.	A summary sheet was written and placed on top of the information sheet, which just mentions the main points of the study. Changes have been made to the information sheet by a member of the group to increase its clarity.
Too much jargon was being used in information sheet (e.g. Computed tomography scan, Magnetic resonance scan)	Terms like "CT scan" and "MRI scan" were replaced with "brain scan".
Participants may be suspicious of what we will use their saliva for.	It was made very clear that the saliva will only be used for one purpose and what that purpose is.
Asking someone to take part in a research project only a few days after their stroke was considered to be too soon. They might be more inclined to take part if they are asked a week after their stroke. Some felt that waiting at least 3 months was more appropriate.	This was taken into consideration during the recruitment process. Due to the design of the study involving a one month follow-up assessment, the comment about waiting 3 months to recruit participants could not be accommodated.
More people would take part if real collateral benefits to taking part were emphasised.	It was pointed out to participants that if they take part they will get 3 follow-up assessments which they would not otherwise get. At these follow-ups, blood pressure will be checked and they will also have the opportunity to raise any concerns about their health that they may have.

Appendix 14 - Case Definition results and FAS scores for each participant.

Participant ID number	One Month		Six Month		12 months	
	Fulfilled fatigue case definition?	FAS Score	Fulfilled fatigue case definition?	FAS Score	Fulfilled fatigue case definition?	FAS Score
001	No	36	No	17	No	14
002	No	12	N/A	N/A	N/A	N/A
003	N/A	N/A	No	19	No	15
004	No	16	No	14	Yes	21
005	No	35	No	18	No	15
006	N/A	N/A	N/A	N/A	N/A	N/A
007	No	13	No	22	N/A	N/A
008	Yes	39	No	16	No	11
009	Yes	26	N/A	N/A	N/A	N/A
010	No	19	No	17	No	22
011	No	23	No	28	N/A	N/A
012	No	18	No	19	No	17
013	No	16	Yes	22	N/A	N/A
014	N/A	N/A	N/A	N/A	N/A	N/A
015	No	17	No	18	N/A	N/A
016	Yes	33	Yes	26	N/A	N/A
017	No	42	N/A	N/A	N/A	N/A
018	Yes	22	N/A	N/A	N/A	N/A
019	No	23	No	18	No	24
020	No	29	Yes	24	No	31
021	No	33	No	26	No	27
022	No	27	No	36	N/A	N/A
023	Yes	22	N/A	N/A	N/A	N/A
024	No	19	No	22	No	24
025	N/A	N/A	N/A	N/A	N/A	N/A
026	No	18	No	22	No	19
027	Yes	30	No	24	No	24
028	No	24	N/A	N/A	N/A	N/A
029	No	12	No	15	No	14
030	No	15	N/A	N/A	N/A	N/A
031	No	41	No	15	No	30
032	No	13	No	17	N/A	N/A
033	No	24	No	20	No	21
034	N/A	N/A	N/A	N/A	N/A	N/A
035	No	17	Yes	41	No	36
036	N/A	N/A	N/A	N/A	N/A	N/A
037	Yes	23	No	15	No	14
038	Yes	16	No	13	No	16
039	Yes	32	No	19	No	30
040	Yes	24	N/A	N/A	N/A	N/A
041	No	12	N/A	N/A	N/A	N/A
042	N/A	N/A	No	19	No	19
043	N/A	N/A	N/A	N/A	N/A	N/A
044	N/A	N/A	N/A	N/A	N/A	N/A
045	No	13	Yes	22	Yes	20
046	No	18	No	17	No	20
047	No	28	No	25	No	23
048	No	16	N/A	N/A	N/A	N/A

049	N/A	N/A	N/A	N/A	N/A	N/A
050	Yes	28	No	25	No	23
051	No	30	N/A	N/A	N/A	N/A
052	Yes	29	Yes	46	Yes	40
053	Yes	49	N/A	N/A	No	24
054	No	24	No	20	No	18
055	No	18	No	24	N/A	N/A
056	Yes	16	N/A	N/A	N/A	N/A
057	No	25	Yes	28	No	25
058	No	16	No	10	No	10
059	No	22	N/A	N/A	N/A	N/A
060	No	19	No	18	No	22
061	N/A	N/A	N/A	N/A	N/A	N/A
062	Yes	26	N/A	N/A	N/A	N/A
063	Yes	29	N/A	N/A	N/A	N/A
064	No	11	No	18	No	10
065	Yes	24	No	21	N/A	N/A
066	N/A	N/A	N/A	N/A	N/A	N/A
067	Yes	39	No	14	No	18
069	No	16	No	15	No	15
070	No	16	N/A	N/A	N/A	N/A
071	No	23	No	26	Yes	29
072	No	17	No	12	No	12
073	Yes	39	Yes	38	Yes	31
074	Yes	36	N/A	N/A	N/A	N/A
076	Yes	33	Yes	28	Yes	29
077	Yes	24	No	25	Yes	31
078	No	21	No	25	No	10
079	No	20	N/A	N/A	N/A	N/A
080	N/A	N/A	N/A	N/A	N/A	N/A
081	Yes	24	No	21	No	19
083	Yes	27	N/A	N/A	N/A	N/A
084	N/A	N/A	N/A	N/A	N/A	N/A
085	No	11	No	15	No	15
086	No	15	No	12	No	19
087	No	34	N/A	N/A	N/A	N/A
088	No	24	No	22	Yes	24
089	Yes	32	N/A	N/A	N/A	N/A
090	Yes	34	Yes	21	No	32
091	No	17	N/A	N/A	N/A	N/A
092	Yes	24	Yes	35	Yes	23
093	No	21	No	16	No	10
094	No	36	N/A	N/A	N/A	N/A
095	No	27	No	24	No	29
096	Yes	23	Yes	32	Yes	25
097	No	28	No	19	N/A	N/A
098	No	24	Yes	20	No	22
099	Yes	25	N/A	N/A	N/A	N/A
100	Yes	33	N/A	N/A	N/A	N/A
101	Yes	28	No	26	No	26
102	No	21	No	22	N/A	N/A
103	Yes	22	No	28	No	13
104	Yes	33	Yes	34	Yes	28
105	No	23	No	13	No	15
106	No	19	No	17	No	27

107	Yes	34	No	38	Yes	41
108	No	25	No	14	No	24
109	No	18	No	23	No	15
110	No	22	No	23	No	28
111	No	29	No	18	Yes	28
112	No	16	No	18	No	20
114	Yes	28	N/A	N/A	N/A	N/A
115	No	23	No	17	No	25
116	No	19	No	17	No	24
117	Yes	33	No	24	No	18
118	Yes	25	Yes	30	N/A	N/A
119	N/A	N/A	No	17	N/A	N/A
120	No	23	No	15	No	18
121	No	18	No	14	No	20
122	No	20	Yes	20	Yes	26
123	N/A	N/A	N/A	N/A	N/A	N/A
124	N/A	N/A	N/A	N/A	N/A	N/A
125	No	14	No	12	N/A	N/A
126	No	23	No	23	No	22
127	N/A	N/A	N/A	N/A	N/A	N/A
128	No	20	No	19	No	20
129	Yes	31	No	24	Yes	31
130	Yes	34	No	28	No	30
131	Yes	19	No	38	No	21
132	Yes	41	N/A	N/A	N/A	N/A
133	No	17	Yes	21	No	23
134	No	27	Yes	25	No	22
135	No	21	N/A	N/A	N/A	N/A
136	No	25	Yes	45	Yes	38
137	N/A	N/A	N/A	N/A	N/A	N/A
138	No	14	No	14	No	17
139	No	22	No	17	No	13
140	No	23	Yes	22	No	29
141	No	26	Yes	44	No	48
142	No	38	No	30	Yes	39
143	N/A	N/A	N/A	N/A	N/A	N/A
144	No	37	Yes	37	No	32
145	No	22	No	22	No	25
146	No	27	No	29	N/A	N/A
147	Yes	47	N/A	N/A	N/A	N/A
148	No	30	No	24	N/A	N/A
149	No	14	N/A	N/A	No	15
150	No	18	No	20	No	17
151	No	26	No	20	No	22
152	N/A	N/A	N/A	N/A	N/A	N/A
153	No	19	No	22	No	28
154	Yes	33	Yes	42	Yes	42
155	No	38	No	26	No	28
156	N/A	N/A	N/A	N/A	N/A	N/A
157	N/A	N/A	N/A	N/A	N/A	N/A
158	No	13	No	13	No	13
159	N/A	N/A	N/A	N/A	N/A	N/A
160	N/A	N/A	No	17	No	15
161	No	10	No	10	No	10

Participants 068, 075, 082 and 113 were excluded as it was discovered after recruitment that they had not had a stroke.

Appendix 15 - Published paper "Exploratory longitudinal cohort study of associations of fatigue after stroke"

The full reference for this paper is: Duncan F., Lewis S.J., Greig C.A., Dennis M.S., Sharpe M., MacLullich A.M.J., and Mead G.E. (2015) Exploratory longitudinal cohort study of associations of fatigue after stroke. *Stroke.* 46(4), pp 1052-1058.

Abstract

Background and Purpose: The aetiology of post-stroke fatigue is unclear. In this prospective study we explored whether reduced physical activity might contribute to post stroke fatigue, or be a consequence of it.

Methods: Patients with a recent acute stroke were assessed at one month, 6 months and 12 months with, Fatigue Assessment Scale (FAS), a fatigue case definition, Hospital Anxiety and Depression Score, sleepiness, quality of life and accelerometry (ActivPAL^{TM}). Bivariate analyses determined associations between fatigue and step count at each time point. Multiple linear regression tested whether one month step count independently predicted 6 and 12 months FAS.

Results: 136 participants (mean age 72 years, 64% men) attended at least one assessment. ActivPAL data were available for 84 (64%), 69 (66%) and 58 (64%) participants at one month, six months and 12 months respectively. At six and 12 months, a positive fatigue case definition was associated with lower daily step counts (p=0.014 and 0.013 respectively). At one, six and 12 months, higher FAS (more fatigue) was associated with lower step count ($p<0.001$, 0.01 and 0.007), higher depression ($p<0.001$), anxiety scores ($p<0.001$) and sleepiness ($P<0.001$) and poorer quality of life ($p<0.001$). Lower daily step count ($p<0.002$ and 0.006) and greater anxiety ($p<0.001$ for both) at one month independently predicted higher FAS at six and 12 months.

Conclusions:

Lower step counts at one month independently predicted greater FAS for up to 12 months. Physical activity might be a therapeutic target for post-stroke fatigue.

Introduction

Fatigue can be defined as a chronic and subjective "feeling of lack of energy, weariness and aversion to effort" [1]. Fatigue after stroke affects around half of stroke survivors, it may persist, [2] it can adversely affect physical and psychological functioning[3] , social and family life [4], health-related quality of life [5, 6,7] and return to paid employment [4, 8].

The aetiology of post-stroke fatigue is unclear. One hypothesis is that fatigue might be triggered by physical inactivity, which commonly occurs as a direct consequence of neurological deficits. Physical inactivity leads to physical deconditioning [9 10], thus making physical activity more fatiguing and leading to further avoidance of activity and persistence of fatigue. However, there is a paucity of evidence for or against an association between fatigue and either physical activity or physical fitness[11 12]. If there is an association between post-stroke fatigue and reduced physical activity, independent of other factors previously found to be associated with fatigue (i.e. depression, anxiety, sleepiness and quality of life), this would support the testing of physical activity-based treatments for fatigue.

This study had three main aims: firstly to investigate whether fatigue is significantly associated with directly measured physical activity at one, six and 12 months after stroke; secondly to examine bivariate relationships between physical activity and other patient characteristics at or near baseline and fatigue at later time points; thirdly to discover whether physical activity remained a significant predictor of later fatigue controlling for other independent variables.

Materials and Methods

Study design, setting and participants

This prospective longitudinal cohort study recruited patients with an acute stroke (haemorrhagic or ischaemic) within the previous month, admitted to hospital or seen in outpatient clinic, with post-codes in South Edinburgh, from 1st September 2009 to 30th June 2011[13]. Exclusion criteria were: subarachnoid haemorrhage (unless secondary to an intraparenchymal haemorrhage); medically unstable or dysphasia or cognitive impairment that was severe enough to prevent the patient from giving informed consent and/or completing questionnaires (as judged by the patient's medical team and the researcher).

Standard Protocol Approvals, Registrations, and Patient Consents

Lothian Ethics committee approved the study. All participants gave written, informed consent.

Variables recorded at recruitment

Stroke subtype (Oxfordshire Community Stroke Project Classification (OCSP)) and patient characteristics were extracted from medical records. The researcher performed the Mini-mental State

Examination (MMSE), the National Institute of Stroke Scale (NIHSS), Physical Activity Scale for the Elderly (PASE) questionnaire for pre-stroke physical activity[14] and asked ‘Did you have a problem with fatigue before your stroke?’

Variables recorded at assessments

At one month, six months and 12 months after stroke, participants were assessed in either a clinical research facility, in a hospital ward (if still an inpatient) or at home, with the following measures:

Fatigue Assessment Scale (FAS)

The FAS is a 10-item self-report scale with 10 statements about difference aspects of fatigue, each rated from one to five (1 = never, 2 = sometimes, 3 = regularly, 4 = often, 5 = always) [15]. It is valid and reliable in stroke [16]. A higher score indicates more fatigue.

Fatigue Case Definition

This valid and reliable structured interview used seven “probe” questions to identify clinically significant fatigue [13,17]. The interviewer ascertains from the responses to these questions whether the participant had experienced fatigue or loss of energy or increased need to rest (as opposed to lack of motivation boredom), every day or nearly every day for at least a two week period in the past month, for at least 50% of waking hours. The fatigue had to interfere with everyday problems or be perceived as a problem. Previous studies have shown that patients fulfilling the case definition have higher FAS scores [13, 17]

Free living physical activity

Time spent sitting or lying, standing upright, stepping and the number of steps per day were directly measured using an accelerometer (ActivPAL™) attached to the thigh unaffected by the stroke. The ActivPAL was chosen as we had previous experience using it in frail older people. After 7 days, the researcher removed it from inpatients. Patients at home returned it by post in pre-paid envelope. Participants were asked to wear the ActivPAL even if they were unable to walk. The first and last days of recording which were incomplete 24 hour recordings were excluded, and data from the middle calendar days only were used. Mean number of steps per day for each participant was calculated.

Hospital Anxiety and Depression Scale (HADS)

This self-report questionnaire has seven items for anxiety and seven for depression. Each item is scored from 0-3, and the scores added to give total scores for anxiety and for depression. HADS was performed because depression and anxiety scores have been reported to be associated with post-stroke fatigue [18].

EuroQol

EuroQol (a quality of life scale)[19] was performed because previous studies had demonstrated an association between quality of life and fatigue after stroke [5, 6, 19]

The Epworth Sleepiness Scale

This scale[20] was used to determine the level of daytime sleepiness as two previous studies have demonstrated an association between the sleep disorders and post-stroke fatigue [21,22]. There are eight items each scored 0 to 3. A score of at least ten suggests a sleep disorder.

Diastolic and systolic blood pressure

These were recorded for patients assessed in the clinical research facility or in hospital (but not at home), because a previous report had shown that fatigue was associated with either high or low blood pressure[23].

Study size

The proposed sample size was 170 at baseline and 120 at the 12 month follow-up, in order to have 92% power to detect a 10% difference in time upright between patients with and without fatigue, according to the case definition, assuming that 40% would have fatigue. The FAS was not used in sample size calculations.

Statistical analysis

SPSS 14.0 and then 19.0 were used. Total FAS was positively skewed and so therefore transformed using logarithmic (base 10) distribution. Missing log FAS values in non-attendees at six and 12 months were replaced using the Expectation Maximisation (EM) single imputation method. Little's MCAR test indicated that the data were missing completely at random (Chi-sq=7.60, p=0.47). This increased the number of valid log FAS values from 105 to 136 at 6 months and from 91 to 136 at 12 months; and thus the number of cases for regression analyses from 69 to 84 at 6 months and from 58 to 84 at 12 months.

Bivariate relationships between fatigue (FAS and case definition) and other variables

Spearman's correlation examined the relationships between log FAS and other patients characteristics at the same time point. For longitudinal relationships over time, Spearman's correlation of log FAS at six and 12 months was performed with possible independent predictors (age, MMSE, NIHSS, BP, EuroQol (UK population preferences, TTO value method), anxiety, depression, sleepiness, time per day stepping, steps per day) at baseline or one month. The relationships between log FAS and gender, stroke characteristics and pre-stroke fatigue was examined with a T Test.

The relationship between the fatigue case definition and gender, stroke characteristics and pre-stroke fatigue was examined using Fisher's exact test, and relationships with age, MMSE, NIHSS, PASE, blood pressure, EuroQol, anxiety, depression, sleepiness and step count using Mann-Whitney U test.

Multivariate analysis

We excluded the presence of non-linearity and extreme outliers on scatterplots and tested the other assumptions for multiple linear regression for the final models.

Multiple regression analyses used log transformed FAS with imputed missing values at six and 12 months as the dependent variables and the mean number of steps per day (in thousands) at one month as the 'baseline' measure of physical activity. Multicollinearity was tested using Variance Inflation Factor (VIF). Other potential independent variables were those with a significant bivariate relationship with log FAS at admission or recruitment (PASE) or at one-month (anxiety, depression and EuroQol). We adjusted models for age at recruitment, gender and pre-stroke fatigue, even though they were not statistically significant, as they were considered of fundamental importance.

Models using time spent stepping were very similar to models with daily step count. We used step count in the final models because it is more often reported in studies of physical activity after stroke[24]. A hierarchical exploratory approach was used initially for entry of predictors into the equations. In the final regression models, all predictors were entered during the same step.

Results

Participants

A total of 382 eligible patients were approached of whom 157 agreed to participate. Of these, 21 (13%) did not attend any assessment visits, leaving 136 patients who are included (table 1). The assessments at one, six and 12 months after stroke onset were attended by 132 (97%), 105 (77%) and 91 (67%) participants respectively (figure). [13]29 (21%) dropped out after the one month assessment (nine died, nine dropped out and gave no specific reason, seven reported being too ill, we were unable to contact four and two had returned to full time work), 15 (11%) dropped out after the six month assessment (three died, seven dropped out, five were too ill and one returned to full time work). There were no significant differences in the characteristics of participants who attended all three assessments compared to those who dropped out at one or six months.

Descriptive data

The proportion of participants fulfilling the fatigue case definition was 43/132 (33%) at one month, 23/105 (22%) at six-months and 18/91 (20%) at 12-months. The median (IQR) FAS score was 23 (18 to 29) at one month, 21 (17 to 25.5) at six months and 22 (17 to 28) at 12 months[13].

ActivPal data were available from 84/132 (63.6%), 69/105 (65.7%) and 58/91 (63.7%) participants at the one, six and 12 month assessments respectively. Reasons for missing ActivPal data included: participants declined (26 at 1 month, 25 at six months and 23 at 12 months), participants attempted to use the device but were unable to e.g. due to skin irritation (6 at one month, and one at 12 months), or devices not returned or malfunctioned (16 at one month, 11 at 6 months and 10 at 12 months). There were at least five days' of ActivPal data for 65 participants at one month, 48 at six months and 44 at 12 months; in the remaining participants there was at least one whole day of activity. The median (IQR) daily step count (thousands) was 2.841 (1.419 to 5.723, n=84) at one month, 4.047 (2.056 to 5.822, n=69) at six months, 4.314 (1.657 to 6.890, n=58) at 12 months. Blood pressure was not obtained in 57 (43%), 49 (47%), 47 (52%) participants at one, six and 12 months respectively, mainly because of assessments at home rather than in hospital.

Bivariate associations with fatigue at each time point

Case definition for fatigue

At one month, there were no significant differences between those with positive and negative case definition for age, MMSE, NIHSS, PASE, blood pressure, anxiety and step count (Mann-Whitney U tests), gender, previous stroke, posterior circulation syndrome stroke (POCS/not POCS), fatigue before stroke, diabetes or hypertension, inpatient/outpatient, side of brain lesion or ischaemic/haemorrhagic stroke (Fisher's Exact tests). Those with a positive fatigue case definition had lower quality of life, greater depression and more sleepiness than those with negative case definition ($p= 0.001$, $p<0.001$ and $p<0.001$, Mann-Whitney U tests).

At six months, quality of life was significantly lower ($p=0.003$) and anxiety, and depression significantly higher ($p=0.014$ and $p=0.010$) in those with a positive case definition (Mann-Whitney U tests). This was also found at 12 months (p values <0.001, 0.020 and 0.015 respectively). More sleepiness was significantly associated with a positive case definition at six months but not at 12 months ($p<0.001$ and $p = 0.054$). Step count was significantly lower in patients with a positive case definition at six and 12 months (median (IQR) step count (thousands) (table 2).

FAS

Associations between log FAS and activity, quality of life, sleepiness, anxiety and depression are presented in table 3. Blood pressure was not significantly related to log FAS at any time point (Spearman's correlations). There were no significant differences in log FAS at any assessment for gender, side of brain lesion, history of diabetes or hypertension, ischaemic/haemorrhagic stroke, inpatient/outpatient, previous stroke or pre-stroke fatigue (t-tests).

Bivariate associations with fatigue (log FAS) over time

Less time spent stepping, lower step count, lower PASE and lower quality of life, higher anxiety and higher depression scores were significantly associated with higher FAS at both six and 12 months (please see Table e1 at http://stroke.ahajournals.org). The marginal significance for diastolic blood pressure should probably be disregarded as a large number of correlations were carried out.

Multiple regression analyses (Table 4)

Scatter plots showed no extreme outliers and no evidence of non-linearity. We intended to explore the influence of physical activity on fatigue, controlling for other patient characteristics using logistic regression with the fatigue case definition as the outcome variable and multiple linear regression with FAS as the outcome variable. There were insufficient events per covariate by 12 months (based on '10 events per covariate' guidance)[25] for logistic regression. We performed multiple linear regression with FAS as planned.

Eighty-four participants were included. Fifty-two without activity data were excluded The only significant differences between those with and without activity data were that the NIHSS was higher (more severe stroke) in those without activity data (table 1).

In the final model, PASE and EuroQol were not significant due to multicollinearity with activity and/or anxiety and were not included. Sleepiness was also not significant. Lower daily step count at one month was significantly associated with higher FAS at six and 12 months, after controlling for age, gender, pre-stroke fatigue and anxiety. Greater anxiety at one month was a significant predictor of higher FAS at six and 12 months. The model accounted for about 30% of the variance in FAS (table 4)

Depression is previously known to be related to fatigue. In bivariate analysis, depression was strongly associated with log FAS and highly correlated with anxiety. Multiple regression models that included depression, but not anxiety, had overall poorer fit and the step count was less significant. Depression was a less significant predictor of log FAS than anxiety in the six month model and it was not significant in the 12 month model. Adding depression to a model that included anxiety did not improve fit. These findings are due to the intercorrelation between depression and anxiety.

The first question of the EuroQoL questionnaire asks participants whether they have no problems walking about, moderate problems walking about or whether they were unable to walk. The regression analyses were repeated with this question being added as a separate independent variable. Adding this variable had very little effect on the model fit (R square changed from 31% to 32% at six months and from 27% to 28% at 12 months), walking ability was not a significant predictor of log FAS score at either six or 12 months and the variables steps taken per day and anxiety remained significant predictors at each of the time points. This suggests that measuring activity has substantial added value over walking ability in predicting fatigue at later time points.

The analyses were repeated omitting the non-significant independent variables (age, gender and fatigue before stroke). There was little difference in the results for the other variables or for the overall model.

Repeating the analyses without imputing missing values for the outcome variable, log FAS, also gave similar results.

Casewise diagnostics identified one extreme outlier in the 12-month model which was not an error in the data. Omitting this case improved the model fit (R squared increased from 27% to 33%) and the step count became more significant (p decreased from 0.006 to 0.001).

The variance inflation factor (VIF) was within an acceptable range in the final models indicating no strong linear relationships amongst predictors. The Durbin-Watson test for serial correlation between errors found that the residuals were uncorrelated. Plots of standardised residuals with standardised predicted values showed homoscedacity and normally distributed errors.

Discussion

This is the largest study to investigate the association between post-stroke fatigue and physical activity and the first longitudinal study to our knowledge to show that lower physical activity and higher anxiety at one month independently predicted greater fatigue at six months and 12 months. Although this statistical ‘prediction’ cannot prove causality, our findings are consistent with the hypothesis that physical inactivity and anxiety might contribute to greater fatigue over time. To be certain about direction of the relationship between fatigue and activity or anxiety , a randomised controlled trial of increasing physical activity, and reducing anxiety after stroke would be needed, with fatigue as an outcome measure.

Three previous cross-sectional studies did not find associations between fatigue and activity[11], possibly because of limitations in statistical power. A meta-analysis of data from 19 observational studies reported significant associations between fatigue and low mood but a non-significant association with anxiety[26]. Our observation that higher anxiety predicts subsequent increased fatigue supports a hypothesis that reducing anxiety might reduce fatigue. If physical activity improves fatigue, there are several putative mechanisms. It may improve aerobic fitness and muscle strength thus enabling a person to perform physical activity without feeling tired. It may improve self-esteem, self-efficacy and social interactions [27,28,29]. Exercise reduces cerebral infarct volume and improves neurobehavioural scores in animal models of focal ischaemia[30] and so exercise might be able to promote brain recovery and possibly improve fatigue[31].

Our data are generalizable to medically stable patients with a mild stroke. There were some limitations. Just under a half of eligible patients agreed to take part, we recruited 93% of our target and our drop-out rate was higher than expected. Some patients declined to use the ActivPAL and of those who used it, data were not obtained in all participants. NIHSS scores were higher in participants without activity data. Severity of stroke may confound the relationship between fatigue and inactivity and so our results may not apply to the whole stroke population. There were insufficient patients fulfilling the fatigue case definition to perform logistic regression, partly because the proportion with fatigue was lower than expected. Consequently comparisons between those who were fatigued and not fatigued should be interpreted with caution especially at the 12 month time point where the case definition was fulfilled in only 18 participants. As planned, we also used FAS as the dependent variable in a multiple regression analysis. We did not specifya cut-off score on the FAS to define the presence or absence of fatigue; however a relationship between FAS score and clinically significant fatigue has been shown in previous studies suggesting that a higher FAS has relevance for a clinical diagnosis[13, 17] ActivPAL would not have detected swimming or cycling, may have undercounted steps in patients with slow or shuffling gaits and would not have differentiated walking at different inclines (requiring different energy expenditure). However, these factors should not have introduced bias unless the amount of unrecorded or more strenuous activity was influenced by the level of fatigue. Participant may have increased their activity levels because they knew they were being monitored. However it is unlikely this would have influenced activity levels for more than a day or so[32], and we followed the standard practice for monitoring activity. The median step count per day was similar to a recent meta-analysis of step counts after stroke[21], and is lower than in a healthy older population. Our single question for pre-stroke fatigue may have been subject to recall bias and does not measure the severity of fatigue or whether their fatigue had been clinically significant. We are aware of only three previous studies of post-stroke which reported the presence of pre-stroke fatigue, so our data, albeit imperfect, is a useful addition to the literature [13,33,34].

Only about 30% of the variance in the FAS was accounted for, suggesting that other unknown factors are associated with fatigue. One recent study demonstrated an association between fatigue and attentional deficits[35]. Other potentially relevant aetiological factors such as coping style, locus of control, poor sleep and systematic inflammation should be explored in future studies.

There are implications for clinical practice and future research. Further work to enhance compliance rates of accelerometer in stroke would be useful, though our compliance rates were substantially higher than has been previously reported.[36] Even though this longitudinal study cannot establish causal influence, it is reasonable for health professionals to encourage patients to increase activity to reduce later fatigue, particularly as the health benefits of physical activity are well-established. Longitudinal cohort studies of post-stroke fatigue should record physical activity and explore mechanisms by which activity might be associated with less fatigue. We also need to better understand the nature of anxiety after stroke and how this might relate to the onset of fatigue. Randomised controlled trials of interventions to reduce anxiety and increase activity should be tested for post-stroke fatigue.

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Figure Legend

Number of participants who attended each assessment and number lost to follow-up.

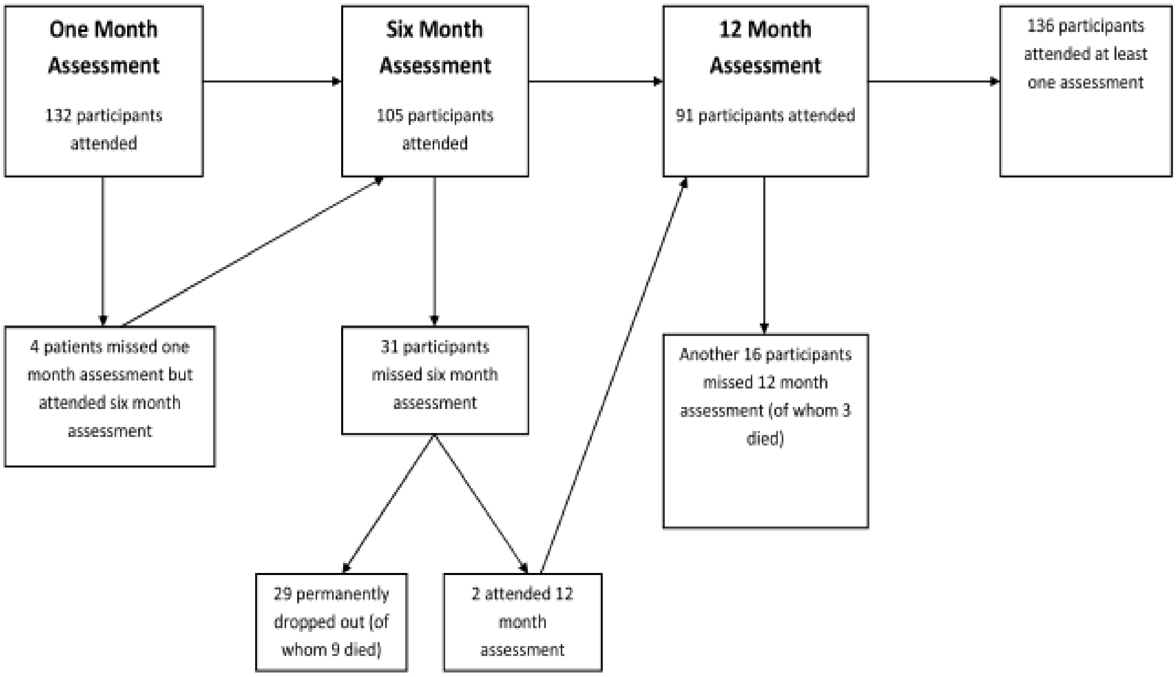

Table 1. Characteristics at recruitment of participants who attended at least one assessment and those who were included in multiple regression analyses after replacement of missing FAS data

Characteristic at recruitment	**Participants who attended at least one assessment (N=136)**	**Participants included in regression analyses (N = 84)**
Median age, years (IQR)	71.8 (62.6 -79.2)	72.3 (65.2-80.5)
Male (%)	88 (64.7)	56 (66.7)
First ever stroke (%)	106 (77.9)	67 (79.8)
Inpatient (%)	124 (91.2)	75 (89.3)
Ischaemic stroke (%)	127 (93.4)	81 (96.4)
Right hemisphere (%)	67 (54.5), n=123	41 (55.4), n=74
Oxford Community Stroke Project class:		
TACS[a] (%)	5 (3.7)	4 (4.8)
PACS[b] (%)	57 (41.9)	29 (34.5)
LACS[c] (%)	40 (29.4)	26 (31.0)
POCS[d] (%)	34 (25.0)	25 (29.8)
Answered 'yes' to: 'Did you have fatigue before your stroke?' (%)	57 (41.9)	36 (42.9)
History of diabetes (%)	23 (16.9)	15 (17.9)
History of hypertension (%)	71 (52.2)	41 (48.8)
Median MMSE[e] (IQR)	27 (25-28.5), n=121	27 (25-29), n=72
Median NIHSS[f] (IQR)	2 (1-4), n=134	2 (1-3), n=82
Median PASE[g] (IQR)	96 (57-158), n=135	96 (59-158), n=83
Mean systolic admission BP (SD)	147.6 (26.5), n=129	149.0 (28.6), n=79
Mean Diastolic BP at admission (SD)	79.9 (14.9), n=129	78.2 (14.4), n=79

[a]TACS=total anterior circulation syndrome, [b]PACS=partial anterior circulation syndrome,
[c]LACS=lacunar syndrome, [d]POCS=posterior circulation syndrome
[e]MMSE Mini Mental State Examination [f]NIHSS National Institute of Health Stroke Scale
[g]PASE Physical Activity Scale for the Elderly

Table 2. Relationship of step count (thousands) to fatigue case definition at three time points

Case definition	Assessment		
	One month	Six months	12 months
Fatigued Median (IQR)	2.48 (0.79 to 4.55) n=24	2.32 (0.87 to 3.65) n=14	2.64 (0.53 to 3.39) n=11
Non-fatigued Median (IQR)	3.42 (1.64 to 5.95) n=60	4.62 (2.40 to 7.29) n=55	4.75 (2.94 to 7.53) n=47
Mann-Whitney U test statistic	888.000	550.000	379.000
P	0.096	0.014	0.013

Table 3. Spearman's correlation of log FAS with other variables at individual time points

Characteristic recorded at one, six & 12 months	**Assessment**								
	1 month			**6 months**			**12 months**		
	coeff	p	n	coeff	p	n	coeff	p	n
Time per day sitting & lying	.35	.001	84	.19	.12	69	.23	.08	57
Time per day upright	-.31	.004	84	-.09	.48	69	-.10	.47	57
Time per day stepping	-.39	<.001	84	-.31	.009	69	-.37	.005	57
Steps per day (thousands)	-.39	<.001	84	-.31	.01	69	-.35	.007	58
Anxiety (HADS)*	.50	<.001	132	.52	<.001	105	.59	<.001	91
Depression (HADS)	.53	<.001	132	.59	<.001	105	.59	<.001	91
EuroQoL	-.49	.001	132	-.54	.001	105	-.61	.001	91
Walking ability	.36	<.000	132	.339	<.000	105	.391	<.000	91
Sleepiness	.40	<.001	132	.414	<.001	105	.514	<.001	91

*HADS - Hospital Anxiety and Depression Scale

Table 4. Multiple linear regression models for the analysis of the relationship between physical activity (mean steps per day) at one month and fatigue at 6 months and 12 months, controlling for age, gender, fatigue before stroke and anxiety.

Predictor	**Dependent variable – FAS* (log 10) at 6 months (n=84)**				**Dependent variable – FAS* (log 10) at 12 months (n=84)**			
	b	SE b	beta	p	b	SE b	beta	p
Constant	1.27 (1.06, 1.49)	.11		<.001	1.25 (1.01, 1.49)	.12		<.001
Age (years)	.000 (-.002, .003)	.001	.030	.76	.001 (-.001, .004)	.001	.10	.34
Gender	.014 (-.043, .072)	.029	.050	.62	-.005 (-.069, .058)	.032	-.018	.86
Fatigue before stroke	-.014 (-.067, .039)	.027	-.051	.60	-.031 (-.09, .028)	.029	-.11	.30
Thousands of steps/day at one month	-.013 (-.021, -.005)	.004	-.32	.002	-.012 (-.021, -.004)	.004	-.29	.006
Anxiety (HADS) at one month	.015 (.008, .022)	.003	.44	<.001	.014 (.007, .022)	.004	.40	<.001
R squared	.31				.27			
	Maximum Variance inflation factor (VIF) 1.15 Durbin-Watson=2.37				Maximum VIF=1.15 Durbin-Watson=2.14			
Extreme outliers	None				One extreme outlier at 12 months (standardised residual -3.23).			

***FAS - Fatigue Assessment Scale**

Appendix 16 - Distributions of characteristics recorded and details of transformations used.

	Distribution before transformation	Transformation Performed	Result of Transformation
Activity Data One month			
-Time spent sitting/lying	Normally distributed	No transformation required	N/A
-Time spent upright	Normally distributed	No transformation required	N/A
-Time spent stepping	Positively skewed	Log transformation	Data now normally distributed
-Steps taken per day	Positively skewed	SQRT transformation	Data now normally distributed
Six months			
-Time spent sitting/lying	Normally distributed	No transformation required	N/A
-Time spent upright	Normally distributed	No transformation required	N/A
-Time spent stepping	Normally distributed	No transformation required	N/A
-Steps taken per day	Normally distributed	No transformation required	N/A
12 months			
-Time spent sitting/lying	Normally distributed	No transformation required	N/A
-Time spent upright	Normally distributed	No transformation required	N/A
-Time spent stepping	Positively skewed	Log transformation	Data now normally distributed
-Steps taken per day	Normally distributed	No transformation required	N/A
	Distribution before transformation	**Transformation performed**	**Result of transformation**
Fatigue Assessment Scale (FAS) scores.	Positively skewed	Log-10 transformation	Data now normally distributed.
Depression and Anxiety (HADS scores)	Positively skewed	Log, square root and reciprocal transformations.	All transformations were unsuccessful. Data still not normally distributed.
EuroQoL	Negatively skewed	Log, square root and reciprocal transformations	All transformations were unsuccessful. Data still not normally distributed
Epworth Sleepiness Scale	Positively Skewed	Square root transformation	Data now normally distributed
Hand grip strength	Normally distributed	No transformation required	N/A
Leg Strength	Normally distributed	No transformation required	N/A
Leg Power	Normally distributed	No transformation required	N/A

Distance walked in six minutes	Positively skewed at one and six months. Normally distributed at 12 months	Log, square root and reciprocal transformations No transformations required	All transformations were unsuccessful. Data are still not normally distributed. N/A
PASE	Positively Skewed	Square root transformation	Data now normally distributed
Age	Negatively Skewed	Reversed square root transformation	Data now normally distributed
NIHSS	Positively Skewed	Log, square root and reciprocal transformations	All transformations were unsuccessful. Data still not normally distributed
MMSE	Negatively Skewed	Log, square root and reciprocal transformations	All transformations were unsuccessful. Data still not normally distributed
Social deprivation	Uniformly distributed	Log, square root and reciprocal transformations	All transformations were unsuccessful. Data still not normally distributed

Please note: unless specified otherwise, skewedness status is same across all three time points. In the final analysis, only the FAS scores were actually transformed and all the independent variables were left untransformed for the purpose of consistency.

Appendix 17 - Spearman's correlations between potential independent variables for regression model.

Characteristic		Anxiety	Depression	Sleepiness	Time spent stepping
Anxiety	Coefficient p-value N		0.558 <0.0001 132	0.387 <0.0001 132	-0.146 0.185 84
Depression	Coefficient p-value N	0.558 <0.0001 132		0.285 0.001 132	-0.333 0.002 84
Sleepiness	Coefficient p-value N	0.387 <0.0001 132	0.285 0.001 132		-0.352 0.001 84
Time spent stepping	Coefficient p-value N	-0.146 0.185 84	-0.333 0.002 84	-0.352 0.001 84	
Steps taken per day	Coefficient p-value N	-0.152 0.168 84	-0.334 0.002 84	-0.365 0.001 84	0.993 <0.0001 84
Quality of life (EuroQoL)	Coefficient p-value N	-0.426 <0.0001 132	-0.523 <0.0001 132	-0.382 <0.0001 132	0.457 <0.0001 84
PASE	Coefficient p-value N	-0.081 0.359 131	-0.201 0.021 131	-0.032 0.714 131	0.569 <0.0001 83
Log-transformed FAS score	Coefficient p-value N	0.496 <0.0001 132	0.531 <0.0001 132	0.400 <0.0001 132	-0.392 <0.0001 84

Characteristic		Steps taken per day	Quality of life (EuroQoL)	PASE	Log-transformed FAS score
Anxiety	Coefficient p-value N	-0.152 0.168 84	-0.426 <0.0001 132	-0.081 0.359 131	0.496 <0.0001 132
Depression	Coefficient p-value N	-0.334 0.002 84	-0.523 <0.0001 132	-0.201 0.021 131	0.531 <0.0001 132
Sleepiness	Coefficient p-value N	-0.365 0.001 84	-0.382 <0.0001 132	-0.032 0.714 131	0.400 <0.0001 132
Time spent stepping	Coefficient p-value N	0.993 <0.0001 84	0.457 <0.0001 84	0.569 <0.0001 83	-0.392 <0.0001 84
Steps taken per day	Coefficient p-value N		0.471 <0.0001 84	0.561 <0.0001 83	-0.393 <0.0001 84
Quality of Life (EuroQoL)	Coefficient p-value N	0.471 <0.0001 84		0.307 <0.0001 131	-0.494 <0.0001 132
PASE	Coefficient p-value N	0.561 <0.0001 83	0.307 <0.0001 131		-0.268 0.002 131
Log-transformed	Coefficient	-0.393	-0.494	-0.268	

FAS score	p-value N	<0.0001 84	<0.0001 132	0.002 131	

Appendix 18 - Leg strength and leg power data for healthy adults.

(Adapted from Skelton et al. 1994, p373)

Age Group	Leg power (watts per kg)	Leg Strength (newtons)
Men		
65-69	2.8 (0.5)	432 (87)
70-74	2.5 (0.4)	414 (80)
75-79	2.3 (0.6)	363 (62)
80-84	1.8 (0.4)	338 (61)
85-89	1.5 (0.4)	305 (63)
Women		
65-69	2.0 (0.6)	290 (71)
70-74	1.6 (0.5)	305 (68)
75-79	1.5 (0.6)	247 (38)
80-84	1.4 (0.6)	226 (46)
85-89	1.2 (0.4)	194 (43)

Appendix 19 - Hand grip strength for health adults.

(Adapted from Bohannon 2006, p 13).

Age Group	Mean left hand kg (95% C.I.)	Mean right hand kg (95% C.I.)
Men		
35-39	51.6 (44.0-59.3)	53.3 (44.0-62.6)
40-44	49.8 (42.5-57.1)	54.1 (47.1-61.2)
45-49	48.7 (40.3-57.2)	50.4 (42.5-58.3)
50-54	45.2 (39.4-51.1)	50.6 (44.2-56.9)
55-59	41.0 (33.7-48.4)	44.1 (36.7-51.4)
60-64	38.7 (33.4-44.0)	41.7 (36.8-46.7)
65-69	38.2 (32.0-42.1)	41.7 (35.4-47.9)
70-74	36.2 (30.3-42.1)	38.2 (32.0-44.5)
75+	29.8 (24.8-34.7)	28.0 (12.7-31.0)
Women		
35-39	30.2 (25.8-34.5)	33.2 (28.6-37.8)
40-44	29.3 (24.5-34.0)	32.8 (28.0-37.6)
45-49	30.8 (25.8-35.7)	33.9 (28.9-39.0)
50-54	28.8 (24.0-33.5)	30.9 (26.7-35.2)
55-59	27.2 (24.6-29.5)	29.9 (26.4-33.6)
60-64	23.0 (18.6-27.3)	25.9 (22.2-29.6)
65-69	22.9 (19.6-26.2)	25.6 (22.5-28.8)
70-74	22.5 (19.1-25.8)	24.2 (20.7-27.8)
75+	16.4 (14.7-18.1)	18.0 (16.0-19.9)

Appendix 20 - Six minute walk test data for healthy adults.

(Adapted from Bohannon 2007, p159).

Age Group	Metres walked in six minutes (mean and 95% C.I.)
60 or over	499 (480-519)
Men	
60 or over	524 (496-553)
60-69	560 (511-609)
70-79	530 (482-578)
80-89	446 (385-507)
Women	
60 or over	475 (448-503)
60-69	505 (460-549)
70-79	490 (442-538)
80-89	382 (316-449)

Appendix 21 - Daily step counts for healthy adults.

(Adapted from Field et al. 2013, p10).

Study	Mean age (SD)	Mean daily step count (SD)
Alzahrani et al. 2009	69 (7)	10346 (3590)
Fulk et al. 2010	65.3 (8.5)	6294 (1768)
Manns et al. 2009	54 (3)	14730 (4522)
Zalewski et al. 2011	68.1 (7.0)	6378 (2149)

Appendix 22 - Ethical Approval Letter

Lothian NHS Board

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Lothian Local Research Ethics Committee 03

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04 March 2009

Dr Gillian E Mead
Senior Lecturer in Geriatric Medicine
University of Edinburgh
Room F1642
Royal Infirmary
Edinburgh
EH16 4SA

Dear Dr Mead

Full title of study:	**Fatigue after stroke: longitudinal cohort study of frequency, prognosis and relationship with physical activity and physical deconditioning**
REC reference number:	**09/S1103/1**

Thank you for your letter of 27 February 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered by the chair on behalf of LREC 3.

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 the research sites listed on the attached form.

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.

Management permission at NHS sites ("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 is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.