Depression after stroke
natural history, predictors and associations with other health outcomes

Ayerbe Garcia-Monzon, Luis

Awarding institution:
King's College London

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Author: Luis Ayerbe Garcia-Monzon

DEPRESSION AFTER STROKE: NATURAL HISTORY, PREDICTORS AND ASSOCIATIONS WITH OTHER HEALTH OUTCOMES

THESIS

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LUIS MARIA AYERBE GARCIA-MONZON

Division of Health and Social Care Research

King's College London

London

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ABSTRACT OF THIS THESIS

Introduction: Stroke is a leading cause of mortality and disability worldwide. There is limited evidence on the natural history, predictors, and outcomes of depression in the long term after stroke.

Objectives:

-To describe the natural history of depression within 15 years of stroke

-To identify the predictors of depression within 15 years of stroke.

-To identify the health outcomes of post-stroke depression.

Methods: A systematic review and meta-analysis of studies of the natural history, predictors and associated outcomes of post-stroke depression was conducted.

Incidence, prevalence, cumulative incidence, time of onset, duration, and recurrence of depression, within 15 years of stroke were estimated in the population based South London Stroke Register (SLSR).

Predictors and outcomes of depression up to 15 years after stroke were identified.

Results: The systematic review identified 49 studies. The pooled prevalence of depression was 29%. The major predictors of depression included disability and history of depression pre-stroke. The main outcomes of depression were lower quality of life and disability.

The SLSR data analyses showed that the prevalence of depression was around 30% and remained stable within 15 years of stroke, with an annual incidence 7 to 21% and cumulative incidence of 55%.

Depression started shortly after stroke, had a short duration and high recurrence rate.

Variables associated with depression included stroke severity, disability at baseline, depression before stroke, together with disability, social isolation, and cognitive impairment

at follow-up. Depression was associated with mortality, disability, cognitive impairment and lower quality of life at follow-up.

Conclusion: depression is a frequent chronic and recurrent condition after stroke, with higher risk among patients with previous depression and after severe strokes, and it is associated with negative health outcomes in the long term.

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CHAPTER 1: INTRODUCTION

1.1 STROKE

The World Health Organisation defines stroke as rapidly developing clinical signs of focal or global neurological deficit, lasting more than 24 hours or leading to death, with no apparent cause other than of a vascular origin.[1]

Stroke, together with ischaemic heart disease, killed 12.9 million people in 2010, one in four deaths worldwide, compared with one in five in 1990.[2] It has been estimated that annually, about 16 million first ever strokes occur in the world.[3] Stroke causes 9% of all deaths globally and is the second most common cause of death.[2] The age adjusted mortality rate of stroke has gone down from 105.7/100.000 in 1990 to 88.4/100.000 in 2010, showing the effectiveness of the stroke control strategies. However, the number of deaths from stroke has increased globally from 4.6 in 1990 to 5.8 million in 2010. In 1990 stroke was the fifth cause of years of life lost (YLLs) globally but in 2010 it was reported to be the third. Nonetheless, the impact of stroke varied between different geographical regions. While in Easter Sub Saharan Africa in 2010 it was the 14th leading cause of YLLs, it was the first cause in other parts of the world such as East Asia or the second cause of YLLs in Western Europe.[2] The shifting pattern of the number of deaths across time, regions, and age groups is consistent with the three key drivers of change: rising total population, rising average age of the world's population, and the broad epidemiological transition from communicable, maternal, neonatal, and nutritional causes towards non-communicable diseases.[2] The total number of stroke deaths in 48 European countries is currently estimated at 1,239,000 per year.[4]

According to the Global burden of disease study published in 2012,[5] the age adjusted rate of reduced DALYs caused by stroke has decreased globally from 1,622/100.000 in 1990 to

1,484/100.000 in 2010. However, the overall number of reduced DALYs caused by stroke has increased worldwide from 86,010 in 1990 to 102,232 in 2010. Stroke has moved from being the fifth most common cause of reduced DALYs in 1990 to the third in 2010.[5] This ranking varies in different regions of the world. While in Eastern Sub-Saharan Africa Stroke is only the 16th most common cause of reduced DALYs, in East Asia is the first cause, and in Western Europe the third. The global burden of disease has continued to shift away from communicable to non-communicable diseases and from premature death to years lived with disability.[5]

About a quarter of stroke patients die within a month, about a third by six months, and a half by one year.[6] 40% of stroke survivors are left with some degree of functional impairment.[7] It is estimated that 25 to 74% of the 50 million stroke survivors worldwide require some assistance or are fully dependent on caregivers for activities of daily living (ADL).[8]

However, evidence on the long term outcomes of stroke is still very limited.[9 10] The burden of disease is estimated by counting how many years of healthy life are lost due to death and non-fatal illness or impairment.[5] To calculate this, a range of data sources, including disease registers, epidemiological studies, and health surveys, are used, yet the data that inform these estimates for long-term planning are not at all comprehensive.[5 10] Population based studies of long term stroke survivors would generate estimates of long-term outcomes of stroke and would provide a better understanding of the burden of stroke on patients, health services, and populations. Studies of outcomes of stroke could also inform strategies to reduce its impact in the long term.

1.2 DEPRESSION

Depressive disorders are characterized by persistent low mood, loss of interest and enjoyment, and reduced energy.[11 12] Depressive symptoms are continuously distributed in any population but are judged to be of clinical significance when they persistently interfere with normal activities. The fifth edition of the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-V)[13] presented the following diagnostic criteria for depression: At least five of the following symptoms that cause clinically significant impairment in social, work, or other important areas of functioning almost every day for at least two weeks. One of the symptoms must be depressed mood and/or loss of interest or pleasure in life activities.

1. Depressed mood most of the day.

2. Diminished interest or pleasure in all or most activities.

3. Significant unintentional weight loss or gain.

4. Insomnia or hypersomnia.

5. Agitation or psychomotor retardation noticed by others.

6. Fatigue or loss of energy.

7. Feelings of worthlessness or inappropriate guilt.

8. Diminished ability to think or concentrate, or indecisiveness.

9. Recurrent thoughts of death or suicide.

The age adjusted rate of reduced DALYs caused by depression has increased globally from 1,019/100.000 in 1990 to 1,078/100.00 in 2010. The overall number of reduced DALYs

caused by depression has also increased worldwide from 54,010 in 1990 to 74,264 in 2010. Depression has moved from being the 15th most common cause of reduced DALYs in 1990 to the 11th in 2010.[5] This ranking varies in different regions of the world. While major depression in Central Sub-Saharan Africa is only the 17th most common cause of reduced DALYs, in North Africa, Middle East and Andean Latin America is the third cause and in Western Europe the 12th.[5]

Studies of burden and outcomes of depression rely on routine mortality and limited disability data.[5 10] Population based observational studies of patients with depression could improve the estimation of loss of DALYs attributed to mental and behavioural disorders. These studies could also inform strategies to reduce the impact of depression.

Depression is more common in women, in patients with chronic medical disorders, and in patients who have experienced stressful life events (e.g.: the loss of a spouse), functional decline, or social isolation.[14] Several studies conducted in different countries reported a cumulative incidence of depression between 13 and 17% during patients' life time and incidence between 5 and 10%.[15 16] A cohort study observing civil servants in the United Kingdom reported prevalence of depression between 12 and 14% in a 20 years follow-up.[17]

Late-life depression is often undetected or undertreated especially in men and members of ethnic minorities. Reasons for under-treatment include stigma associated with depression, the belief that depression is a normal part of aging, coexisting problems, such as chronic medical disorders, pain, cognitive impairment, and alcohol or substance misuse.[14] Late-life depression that is untreated can last for years and is associated with a poor quality of life, difficulty with social and physical functioning, poor adherence to treatment, worsening of chronic medical problems, and increased morbidity and mortality from suicide and other causes. Effective treatment of late-life depression has been associated with improved emotional, social, and

physical functioning and quality of life. It has also been associated with better self-care for chronic medical conditions and reduced mortality.[14]

Observational studies reporting the natural history of depression, identifying groups at highest risk and evaluating the outcomes of depression in the long term, would contribute to a better understanding of its impact.

1.3 DEPRESSION AND LONG TERM CONDITIONS

All illnesses carry both physical and psychological features.[18] Depression in the physically ill may be a complication of the medical illness, a cause of it, or a coincidental occurence.[19 20] Depressive disorders in the medically ill cause suffering and family disruption, they can exacerbate bodily symptoms, and complicate the patients' care.[11 18]

1.3.1 The relationship between depression and long term conditions

Depression may occur in any patient secondary, directly or indirectly, to the biopsychosocial stress of medical illness.[19 20] It has been postulated that the greater the medical burden the higher the risk of depression. However, patients with preexisting vulnerability are most likely to become depressed on the face of disease.[11 20 21] It could be hypothesized then that depression is not randomly distributed amongst all the physically ill but is more prevalent in those who have previous vulnerability and suffer more severe illnesses.

Therefore, the likelihood of depression depends on factors such as the personal predisposition, the clinical course of the medical disease and the effectiveness of individual coping strategies.[19] Several specific direct and indirect mechanisms for depression associated with physical illness have been proposed.[18-20]

These mechanisms include factors linked to the medical condition. There are risk factors for many physical diseases that are also risk factors for depression for example alcohol misuse or diabetes.[22 23] The onset or diagnosis of the medical disease, the start of treatment, or any changes in prognosis, may also have an effect on the patients' mood.[20 24] In some cases the therapeutic approach may be associated with depression. This would be the case of treatments with some drugs, such as beta blockers or steroids, or the treatment in intensive care, which can lead to depression.[20 25] The pain, either iatrogenic or caused naturally by the disease, any significant medical complications, such as a stroke following an arrythmia, or the long term dependence for activities of daily living, can also have a negative effect on patients' mood.[26 27] The uncertain or poor prognosis of the medical disease can lead to depression as well.[18-21]

The involvement of psychological mechanisms for the risk of depression among the medically ill has also been reported.[14 19 20 28 29] A central factor in the psychological response to the illness may be the personal meaning of the illness for the individual. For example some patients experiencing guilt or self-recrimination may interpret the illness as a punishment for their perceived misdeeds.[20] Damaged self steem and dysfunctional attitudes, such as self judgement on unrealistic standards, may also increase the risk of depression.[18 30] Other psychological mechanisms that can lead to depression are cognitive distortions e.g.: overgeneralization of specific poor outcomes, or selective attention focused on negative signs of disease.[20] The lack of factors that can protect against depression, such as positive illusions, may be associated with depressive symptoms as well. Also maladaptive coping strategies, ineffective efforts to manage the demands of the medicall problem, are relevant in the development of depressive symptoms.[19] Other pyschological factors include some types of personality, changes in the sense of identity and alterations in body image for example among patients with disfiguring diseases.[19 20]

Biological mechanisms may also play a role in the association between phisical diseases and depression.[14 29 31] These would include vascular events affecting the brain, directly such as stroke, or indirectly such as coronary atery disease. Medical problems, with or without vascular physiopathology, affecting neurochemical pathways mediating mood may also affect the incidence of depression.[14 18-21 31] It has been proposed that physical pain and depression may have a deeper biological connection than simple cause and effect as serotonin and norepinephrine are neurotransmitters that influence both pain and mood. Therefore, dysregulation of these transmitters may be linked to both depression and pain.[21] Immunological or endocrine disorders such as the ones observed in Graves' disease, may also affect the incidence of depression.[32] Different specific physiopathological mechanisms occurring during the course of various forms of cancer, infections, and vitamin deficiencies have also been proposed to have a role in the development of depression.[19 20]

A number of sociological factors related to the physical disease may have an effect on patients' mood as well.[19] These would include concerns about family and or carers e.g.: difficulties on the education of children depending on the patient. The loss of social roles, stigmatization, isolation, relocation, institutionalisation, finacial worries, the loss of employment or professional status, or other negative life events related to the illnes may increase the risk of depression as well.[33 34] There are also social factors for depression not directly linked to the disease but prevalent in some specific groups of patients, for example the loss of spouse in elderly patients affected by age related diseases.[18-20]

All these factors and mechanisms contribute to the physiological, psychological and sociological changes, furhter increasing susceptibility to depression or triggering depression in already vulnerable individuals.[11 18 20 31] Most of them have been presented

as risk factors, hence associated with an increase of depression, for example social isolation or disability. It could be suggested that the absence of these risk factors, or the presence of others oposite to them, would therefore protect against depression. This would be the case for example of social support, the clinical improvement of the medical problem, or independence for activities of daily living.[19] The medical control of cardiovascular risk would result in a reduction of vascular depression.[11] A high level of education, which is associated with help seeking behaviour and adherence to treatment, is also associated with lower incidence of mood disorders.[12] Healthy lifestyle, such as appropriate diet and sleep, may reduce poor mental health outcomes as well.[35] Exercise has been known to improve general well-being regardless of age, gender, or physical ability. Older adults who exercise regularly report improved mood and self-satisfaction.[35] [36] Other factors that may protect against depression include religiosity and spirituality,[36] [37] and also the development of effective strategies to cope with the medical disease e.g.: reduction of stigmatization, cognitive reframing, and acceptance of the new situation.[36]

Evidence on the nature and the strength of the association of all these factors with depression would help in the identification of patients at risk of depression in the context of a non psychiatric disease. It could also help in the development of interventions which could reduce depressive symptoms among the medically ill.

1.3.2 The associated outcomes of depression in people with long term conditions

Depression in patients with long term conditions is also relevant because its association with poor health outcomes.[38-44] Depression in the elderly is also associated with an increase of health service use and with an increase of the overall healthcare costs.[45]

A number of plausible biobehavioural mechanisms have been hypothesized to underlie the relationship between depression and poor health outcome: lack of treatment adherence; lifestyle factors such as smoking, heavy alcohol use, and physical inactivity; traditional risk factors including hypertension, diabetes, and insulin resistance; changes in platelet reactivity; dysregulation of the autonomic nervous system and hypothalamic pituitary adrenal axis; and alterations in the immune response/inflammation.[46] However, much of the existing evidence for the relationship between depression and poor health is derived from cross-sectional studies,[46 47] with a limited number of prospective papers.[48-50]

It would be plausible that an effective management of depression could improve not only patients' mood but functionality as well, and also reduce the costs of health care.[18 51] An effective management of medical patients with depression may also decrease the incidence of suicide and alcohol misuse, and reduce the number of investigations performed for physical symptoms that actually reflect underlying psychological distress.[18]

1.3.3 The detection of depression in people with long term conditions

In spite of its enormous clinical and public health importance, depressive illness is often underdiagnosed and undertreated, particularly when it coexists with physical illness.[19] Modern medical practice is clearly orientated towards detecting and treating organic disease.[18] It is regarded as a greater error failing to diagnose an organic disorder than a psychological one, even if the later could be alleviated by appropriate treatment. This is in spite of the Hippocratic teaching of the nervous element in the genesis of disease, the awareness of psychological disorders in the writings of physicians, and the experiences reported by patients and the laity over centuries.[18 52] There are some reasons behind the underdiagnosis of depression in the medically ill. These include the arbitrary boundaries

among clinical and non pathological symptoms, the overlap between symptoms of depression and physical disorder, doctors' limited experience with mental health disorders, [18 20] the belief that most patients with medical illness are depressed, the idea that depression is an understandable reaction that does not require treatment, and the belief that treatments for depression are ineffective or hazardous with such patients.[20 53] Depression may also be underreported by patients with physical conditions. Many patients may deny mood disturbance or feel threatened by the suggestion that the problem is a psychological one. Other factors leading to the underreporting of depression include diminished affective awareness, fear of stigma of reporting emotional illnes, and the lack of knowledge about available assitance and/or treatment.[18 20 52]

A good understanding of the distribution of depression, and its consequences, among people with long term conditions may contribute to more effective communication and the timing and targetting of potential new management strategies.

1.3.4 Further research on depression in people with long term conditions

Depressive illness is usually treatable[54 55] and there is no evidence to suggest that tactful questionning about emotional distress is harmful.[19 20] One Cochrane review reported that antidepressants improve depression symptoms among patients with medical conditions.[54] Another one reported that antidepressants appeared to improve disability, neurological deficit and impaired cognition in stroke patients, although further studies to confirm these results are required.[56]

Evidence on the natural history, predictors and outcomes of depression among patients with specific conditions is required to understand the emotional impact of disease in the long term. It is also essential for a better clinical management and the development of innovative

interventions for depression in the medically ill. Further studies should contribute to the identification of patients, and the time points during the course of the physical disease, in which the risk of depression is significant. An updated systematic review of the available literature on depression in specific clinical conditions should be the base of these studies.

1.4 DEPRESSION AFTER STROKE

Stroke is directly or indirectly associated with many of the biological, psychological and sociological factors, discussed in the previous section, that can lead to depression in the medically ill. The long term outcomes of stroke, including disability and lower quality of life,[10] are also common among patients with other long term conditions that according to a number of systematic reviews have a strong association with depression. These include heart failure,[57] diabetes,[22] chronic obstructive pulmonary disease (COPD),[58] and kidney failure.[59] It is therefore accepted that stroke might predispose, precipitate, or perpetuate some late-life depressive syndromes.[24]

A meta-analysis of observational studies published in 2005 reported the pooled prevalence of depression at any time after stroke to be 33% (95% CI 29-36%).[60] Studies that have compared the post-stroke incidence of depression with that in appropriately matched community controls have found that the risk of depression is at least doubled after stroke compared with what would be expected in the general population.[61] A systematic review, also published in 2005, reported four main variables associated with, or predictive of, depression after stroke: stroke severity, cognitive impairment, physical disability and social isolation.[62] Studies included in both reviews have limitations including: small samples, patients only being assessed once, short follow-up and weak analysis. While some research on this topic may have been published since 2005, there are no updated reviews of the incidence,

prevalence, natural history and predictors of depression after stroke that include the more recent studies.

Depression after stroke is important not only because of the distress it causes for patients and their families, but because of its possible association with other negative health outcomes including increased mortality, severe physical impairment and functional dependence.[63-73] However, the evidence on the association between depression and other health outcomes is limited: most studies have small sample size and short follow-up; the nature of the associations between depression and some outcomes is unclear as depression could be the cause or the result of them; measurements of depression might be confounded by somatic symptoms caused by stroke itself; stroke on its own may also be responsible for some of these outcomes. A recent study reviewed prevalence, predictors and outcomes of depression within a month of stroke.[74] However there are no updated systematic reviews summarising the associations between depression after stroke and other health outcomes in the long term.

A majority of long-term stroke survivors with emotional needs reported that they did not receive adequate help to deal with them.[75] Clinical guidelines recommend that stroke patients should be screened for depression and those patients who have depression sufficient to cause distress and/or to impede rehabilitation should be assessed clinically for further treatment.[76 77] However, two Cochrane reviews [78 79] reported that the effect of available preventive and therapeutic measures for depression after stroke is limited. The authors of these reviews questioned if treatments had been given for long enough, starting at the right time, and to the patients who actually needed to be treated. The poor epidemiological evidence in which interventions were based may have led to an underestimation of their real effect.

Population based observational studies of depression among stroke survivors would provide a better estimation of its impact on patients, health services and populations in the long term.

The year-on-year estimates describing natural history of depression after stroke, reported in observational studies, could be used to provide more precise estimations in future calculations of Global Burden of Disease. It is rare that population-based studies observe outcomes in such a prospective manner, with over ten years of follow-up.[10] Observational studies would also help to understand the nature and the strength of the association between stroke and depression. Furthermore, these studies could help in the development of strategies for an effective management of depression afters stroke.

An epidemiological design of future studies would provide a holistic approach to depression after stroke. Evidence on the natural history, predictors and associated outcomes of depression after stroke, produced in these studies should be easily applicable in clinical medicine, public health and health policy. It may also inform other studies approaching this topic with different methods, e.g.: neuroradiology or neurobiology studies.

Findings on stroke populations may also help to understand the association between depression and other diseases, such as heart failure or COPD, which have outcomes in common with stroke.

It has been reported that patients with multiple disease often receive care from different teams in a disjointed way resulting in uncoordinated care, multiple different hospital visits, and sometimes confusing or contradictory information. This happens both in hospitals and in the community.[80] A better understanding of the natural history predictors and outcomes of depression after stroke could help to co-ordinate and integrate an approach to depression, which is also an outcome observed in patients with other long term conditions.[22 57-59 81]

Finally, observations of depression in stroke patients may also be useful in the management of depression in the context of diseases which are less frequent or have received less attention from researchers than stroke e.g.: polyneuropathies or myopathies.

1.5 THEORETICAL FRAMEWORK AND HYPOTHESIS OF THIS THESIS

As discussed in previous sections stroke is a leading cause of mortality and disability worldwide. Depression is also an important cause of loss of DALYs globally and it has an increased prevalence among patients with long term conditions including stroke. The association between a medical long term condition and depression is complex and includes factors directly associated with the diseases, for example case severity and poor prognosis, psychological factors such a low self-esteem, biological mechanisms such as neurological damage, sociological factors for example isolation, and ineffective protective strategies.

There is limited evidence on the long term natural history, predictors, and outcomes of depression after stroke. This affects the management of depression in stroke patients that currently has limited effectiveness.

Population based studies, with large sample size, observing a range of outcomes in long term stroke survivors provide the potential sampling frame to study the natural history of depression after a long term condition. An ideal dataset would include previous medical history, sociodemographic data, clinical details of the acute event, and long term clinical data of depression and other outcomes. This would help to estimate the natural history of depression in the long term after stroke. It would also help to observe the strength and the nature of the association between depression and a number of variables present before and

after the acute event. This would result in a better understanding of the impact of depression on stroke survivors and would help in the development of effective management strategies.

Epidemiological studies of depression in the long term after stroke could also help in the estimation of the impact of stroke in populations. Finally, these studies would test some of the links between mental and physical health and therefore, they could also provide evidence applicable in the context of other long term conditions.

The available evidence on the natural history, predictors and outcomes of depression after stroke raises the hypothesis that will be tested in this thesis:

Depression can affect stroke survivors in the long term and it may be associated with other health outcomes.

An updated systematic review of observational studies of the natural history, predictors, and associated health outcomes, of depression after stroke is needed to understand in detail what is already known on this topic, and to identify the gaps in the knowledge. Prospective studies in stroke cohorts will be needed to address the specific research questions arising from the review.

CHAPTER 2: DEPRESSION AFTER STROKE, NATURAL HISTORY, PREDICTORS AND ASSOCIATED OUTCOMES; A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

2.1 ABSTRACT

Objective: To estimate the natural history, predictors and associated outcomes of depression after stroke.

Methods: systematic review and meta-analysis of studies of unselected stroke patients reporting at least one of the following: prevalence, incidence, cumulative incidence, duration, predictors or outcomes of depression after stroke. Studies published up to the 31/08/2011 were searched in MEDLINE, EMBASE, Psyc-INFO and Web of Science.

Results: 49 studies were included, out of the 13,558 references initially found. Most studies had small sample sizes and short follow-up. Pooled prevalence of depression after stroke was 29% (25-32), and remained stable up to ten years after stroke, with a cumulative incidence between 39% and 48% within a year of stroke. 15% to 57% of patients depressed within the first few months after stroke had recovered from depression one year after stroke. Major predictors of depression after stroke were disability and history of depression pre-stroke. Other predictors included stroke severity, cognitive impairment, poor family support, and anxiety. Lower quality of life and disability were health outcomes independently associated with depression after stroke. The association between depression after stroke and higher mortality was also reported.

Conclusions: The natural history of depression after stroke seems to be dynamic. Depression after stroke may be associated with adverse health outcomes and requires periodic clinical attention in the long term that should focus on patients at highest risk. The natural history,

predictors, and associated health outcomes, of depression in the long term after stroke remain unknown. Future studies of high quality are required.

This literature review has been published in the British Journal of Psychiatry

(See Appendix one)

2.2 INTRODUCTION

In this chapter the available studies on frequency, predictors and associated outcomes of depression after stroke will be reviewed to identify what is already known on this topic and what are the gaps in the knowledge.

The specific questions to be addressed by this thesis will arise from the results of this literature review

2.3 METHODS

The recommendations included in the statement Meta-analysis of Observational Studies in Epidemiology (MOOSE)[82] were used to undertake this review and meta-analysis. The Cochrane Collaboration Handbook for Systematic Reviews was also used as a reference to guide the methods of this chapter.[83]

This review includes studies of stroke patients, in whom an assessment of mood was performed at a specific time point, falling into at least one of the following three groups:

1- Studies reporting the proportion of patients who met the diagnostic category of depression, defined by scores above a cut-point on a standard scale, DSM-IIIR[84] DSM-IV [85], DSM-IV TR,[86] or other diagnostic criteria.

2- Studies investigating variables potentially associated with, or predictive of, depression after stroke.

3- Studies investigating the association between depression after stroke and a health outcome observed at a later stage

2.3.1 Search strategy and selection of studies:

Observational studies reporting, prevalence, incidence, cumulative incidence, duration, predictors or outcomes of depression after stroke were searched in the following databases: EMBASE (1947 – August 2011), MEDLINE (1948 – August 2011), PsycINFO (1806 – August 2011), and ISI Web of Science (1900 – August 2011).

The search strategy presented in Figure 2.1, that includes controlled vocabulary and free text terms, was used for EMBASE, MEDLINE and PsycINFO (Ovid), and modified to suit ISI Web of Science.

The search strategy was designed, following the MOOSE[82] and Cochrane[83] recommendations, to be extensive in order to ensure that as many as possible of the necessary and relevant studies were included in the review. The research questions addressed in this chapter focused on results of observational studies; however this concept may not be well described in the title or abstract of an article and is often not well indexed with controlled vocabulary terms. Therefore, the search strategy did not include terms referring to study designs and it included terms for the concept of stroke and depression only. The recommendations of the Cochrane Collaboration regarding search strategies are that is unnecessary, and even undesirable, to search on every aspect of the review's question.[83]

In addition, references of the following previous reviews were checked for relevant studies: Turner-Stokes and Hassan 2002 review on studies of frequency and impact of depression after stroke; [63] Hackett and colleagues 2005 reviews on studies of frequency and predictors of depression after stroke;[60 62] Robinson and Spalletta 2010 review on studies of frequency, predictors and outcomes of depression after stroke; [87] Kouwenhoven and colleagues review on depression in acute stroke, prevalence, dominant symptoms and associated factors.[74]

There were no restrictions on the basis of language, sample size, or duration of follow-up. Studies were excluded if they had selected their participants according to criteria that had not been validated. These included the following: 1) studies limited to specific clinical characteristics (e.g., strokes in specific locations, strokes of a specific subtype); 2) they were limited to specific patient characteristics (e.g., patients of a specific age group); 3) studies of mixed populations (e.g., stroke and head injury) unless separate results for stroke patients were identified; 4) convenience sampling. Although in some cases these ways of selecting participants made these studies feasible, it was considered that estimates produced in these samples could be substantially different from the ones of the real stroke population. It was also acknowledged that including these studies in a meta-analysis together with those of unselected stroke patients could introduce error and make the results difficult to interpret. Other methodological considerations that were used to exclude studies were: 1) unstructured assessment of mood; 2) mood reported only as a continuous variable (not categorising patients as depressed or not depressed); and 3) studies with retrospective recruitment.

Following the Cochrane methodology[83] some of the studies that did not fit the inclusion criteria are also presented. This covers all studies that may on the surface appear to meet the eligibility criteria but on further inspection do not, and also those that do not meet all of the criteria but are well known and likely to be thought relevant by some readers. These studies that are presented do not include however all the reports that were identified by the comprehensive search.

The results of these excluded studies, close to fitting the inclusion criteria, were observed and discussed carefully and they revealed to be very heterogeneous. Such heterogeneity was attributed to the diverse methods used, which included selection of specific groups of patients, non validated ways of assessing for depression and unusual statistical analysis. It was considered very difficult to translate these heterogeneous results into clinical

recommendations or into new research questions that could inform the analysis of the SLSR data. The observation of these results helped to re-asses the inclusion criteria of this review.

While it is acknowledged that no inclusion criteria guarantees the identification of absolutely all the relevant literature, the criteria used in this review were considered appropriate to minimise error. The uniformity of the methods of the included papers provided results which were still diverse but more consistent across studies. This led to clearer clinical recommendations and to the definition of the original research questions that are elaborated in the following chapters. Nonetheless, some of the results and ideas presented in these excluded papers are mentioned in the discussion section of this chapter and they also have been used in the design, methods, and discussion of the studies undertaken in this thesis.

In some cases, similarities between studies indicated the possibility of multiple publications from the same cohort. In the absence of explicit cross-referencing, we considered articles to be from the same cohort if there was evidence of overlapping recruitment sites, study dates, and grant funding numbers, or there were similar reported patient characteristics in the studies. Where several articles reported results from the same population, data were taken from the publication with longest follow-up. When more than one method of assessment for depression was used, the result of the assessment that was discussed more in depth by the authors was included in the meta-analysis. When the prevalence of "major" and "minor" depression was reported separately, they were grouped as depression.

Studies of predictors of depression that were included used depression as a dependent variable in a statistical model where potential predictors were explanatory variables. Studies of outcomes of depression that were included used outcomes as a dependent variable in a model where depression was an explanatory variable. Studies using only univariate analysis were not included as their results could be highly confounded.[88] For studies of predictors or

outcomes, information was collected on all variables analysed as potential predictors, outcomes and confounders.

Only studies reporting outcomes measured at a later time point than depression were included. Information was collected on all of the variables analysed as potential predictors, outcomes and confounders. The quality of studies was assessed according to accepted criteria.[62] Authors of studies were contacted when there were questions about whether papers met the inclusion criteria and also to verify methods and results that may not have been reported.

Search Terms
1. exp Cerebrovascular Disorders/
2. stroke*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
3. poststroke*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
4. cerebrovascular*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
5. cerebral vascular.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
6. 2 or 3
7. 4 or 5
8. infarct*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
9. isch?emi*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
10. thrombo*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
11. emboli*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
12. apoplexy.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
13. 8 or 9 or 10 or 11 or 12
14. cerebral.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
15. intracerebral.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
16. intracranial.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
17. brain*.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
18. cerebellar.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
19. vertebrobasilar.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
20. 14 or 15 or 16 or 17 or 18 or 19
21. h?emorrhage.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
22. bleed.mp. [mp=ti, ot, ab, nm, hw, ui, an, tc, id, sh, tn, dm, mf]
23. 21 or 22
24. 13 and 20
25. 20 and 23
26. 1 or 6 or 7 or 24 or 25
27. Depression/
28. Depressive Disorder/
29. 27 or 28
30. 26 and 29
31. limit 30 to human
32. limit 31 to yr="2000 - 2011"

Figure 2.1: Search strategy

2.3.2 Statistical methods

A meta-analysis was undertaken to obtain pooled estimates of prevalence of depression. Since the different study settings and follow-up periods could introduce heterogeneity a classification of studies was first conducted and a subgroup analysis was then carried out. In the first meta-analysis studies were classified in four categories: "acute phase" (within one month of stroke); "medium-term phase" (one to six months); "long-term phase" (six months to one year); “very long-term” (more than one year after stroke). Second, a meta-analysis was conducted in which studies were classified as population, hospital or rehabilitation studies.

Different models for the meta-analysis, fixed-effect or random-effect, were considered. For a fixed-effect meta-analysis the assumption is made that the observed differences among study results are due solely to the play of chance, e.g.: that there is no statistical heterogeneity. A random-effects meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical, but follow some distribution. The conventional choice of distribution is a normal distribution. It is difficult to establish the validity of any distributional assumption, and this is a common criticism of random-effects meta-analyses. The importance of the particular assumed shape for this distribution is not known. The confidence interval from a random-effects meta-analysis describes uncertainty in the location of the mean of systematically different prevalence in the different studies.[83] After studying its advantages and disadvantages a random-effect model was considered more appropriate for this analysis than the fixed-effect one.

The assessment of patients at an exact time after stroke was judged to be logistically very difficult therefore studies with time of follow-up reported as an interval e.g.: three to nine months, were included in this review. In the meta-analysis they were included in the category of the earliest time point as it was considered to be the least affected by drop out due to

mortality. For example a study reporting estimates obtained between three and nine months would be included in the category of one to six months. Categorisation of these studies according to their mid time point of follow-up was also attempted. For example studies assessing patients between three and seven months after stroke would have been categorised as if all patients had been seen at five months. However, the differences of the estimates using earliest time point and mid time point were found to be negligible. It was considered that the mid time point categorisation would have allowed for higher error introduced by mortality than the categorisation by the earliest time point.

For studies with follow–up assessments at more than one time point only results from the last follow–up were included in the meta-analysis. This was done to obtain pooled estimates of prevalence long term after stroke avoiding the bias that would have been introduced by entering repeated estimates of a study in the same meta-analysis. However, data from measurements at all time points were also recorded and presented in the tables.

A funnel plot was used to investigate possible publication bias.

The number of studies reporting estimates of natural history of depression after stroke other than prevalence (e.g.: incidence) was small. The assessments for depression had been conducted at different time points in each of these studies. Therefore, a meta-analysis to obtained pooled estimates of other measures of natural history was not conducted. Results presented by individual studies were reported separately.

2.4 RESULTS

9799 references were found in EMBASE, MEDLINE and PsycINFO, and another 3859 references were found in ISI Web of science. After removing duplicates, the title of the 12907 remaining studies was read and 505 studies were assessed for inclusion/exclusion

criteria. Finally 49 studies, published between 1983 and 2011, reporting incidence, prevalence, cumulative incidence, duration, predictors or associated outcomes, of depression after stroke were included in this review. (Figure 2.2)

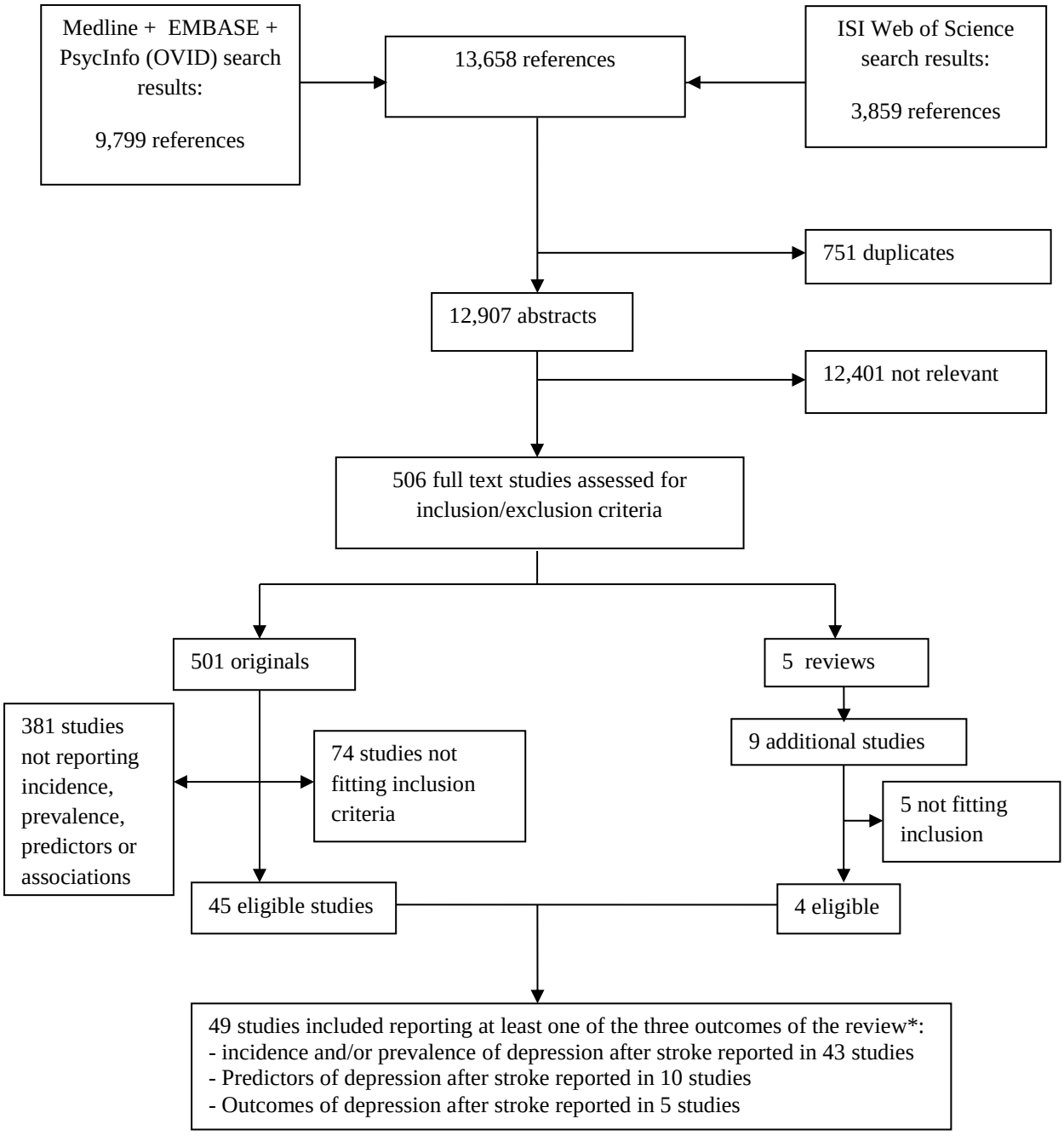


Figure 2.2 Results of the literature search.

*Many studies, together with prevalence of depression after stroke, reported either predictors or outcomes of depression after stroke.

In all the studies included the analyses were based on the result of assessments for depression conducted after stroke, not accounting for whether the onset of depression occurred before or after the stroke.

2.4.1 Natural history of depression after stroke

44 studies, including 20,293 patients, reported prevalence of depression after stroke (Tables 2.1, 2.2 and 2.3). Six of them were population based studies[10 89-93], fifteen were hospital studies[94-108], and 23 were rehabilitation studies.[109-130] The number of patients assessed for depression in each study ranged from 14 to 13,999. Only nine studies assessed more than 200 patients,[10 89 90 92 93 98 107 118 123] and only one of them assessed more than 1,000 patients.[98]

Across the 43 studies, eleven different methods were used to assess depression. 29 studies used validated scales, twelve studies used the Diagnostic and Statistical Manual of Mental disorders (DSM)[85] criteria, and two studies used a validated question. The cut-off points for the same scale used to diagnose depression in different studies were not consistent. Only eight studies reported the prevalence of depression more than one year after stroke, and only thirteen studies assessed patients at more than one time point.

The search also identified several studies reporting rates of depression after stroke, that did not fit the inclusion criteria: 12 studies that excluded patients with haemorrhagic strokes,[71 100 131-140] eight that excluded patients with subarachnoid haemorrhages,[141-148] seven studies that only included patients with supratentorial strokes,[135 149-154], and three studies that excluded patients with more than one lesion.[148 155 156]

In the studies fitting the inclusion criteria, the reported prevalence of depression ranged from 12 to 60%. The pooled prevalence of depression, and its 95% confidence interval (CI), observed at any time point was 29% (25-32), with a prevalence of 28% (23-34) within a

month of stroke, 31% (24-39) at on to six months, 33% (23-43) at six months to one year, and 25% (19-32) at more than one year (Figure 2.3). The pooled prevalence of depression at any time point in population studies was 22% (17-28), in hospital studies 30% (24-36), and 30% (25-36) in rehabilitation studies (Figure 2.4). The prevalence rates did not differ significantly over time or in studies of different settings. Heterogeneity was significant for all investigated categories. The studies using a simple single question to diagnose depression[98 123] reported low prevalence of depression, 14 and 16%. Studies with small sample size tended to report larger estimates of prevalence.

Author Year	Country	Diagnosis	Time since stroke	Assessed (N)	Depressed (n)	Depressed (%)
Wade 1987 [93]	UK	WDI>18	3w	379	84	22
			6m	377	74	20
			12m	348	63	18
House 1991 [91]	UK	BDI>9	1m	76	24	32
			6m	107	34	32
			12 m	88	14	16
Burvill 1995[89]	Australia	DSM-III	4 m	294	68	23
Paul 2006 [157]	Australia	IDA >6	5 y	289	48	17
Chausson 2010 [158]	Martinique	MADRS> 7	5 y	252	65	26
Wolfe 2011[10]	UK	HAD>7	3m	876	289	33
			1y	991	275	28
			2y	743	225	30
			3y	998	315	31
			4y	806	249	31
			5y	569	173	28
			6y	525	163	30
			7y	407	129	32
			8y	334	102	30
			9y	231	87	38
			10y	197	71	36

Table 2.1 Population based studies of Prevalence of depression after stroke

WDI: Wakefield Depression Inventory

BDI: Beck Depression Inventory

DSM: Diagnostic and Statistical Manual of Mental Disorders

IDA: Irritability Depression and Anxiety Scale

MADRS: Montgomery-Åsberg Depression Rating Scale

HAD: Hospital Anxiety and Depression Scale

Author/Year	Country	Diagnosis	Time since stroke	Assessed (N)	Depressed (n)	Depressed (%)
Ebrahim 1987 [97]	UK	GHQ >11	6 m	149	34	23
Knapp 1998 [104]	UK	HAD>7	<1m	30	10	33
			1m after discharge	30	11	37
			6 m	30	8	27
Robinson 1999[106]	USA	DSM-IV	Acute phase	50	22	44
			3-6m	50	20	40
			1-2 y	50	21	42
Gesztelyi 1999 [101]	Hungary	BDI>14	2y	119	13	11
Hayee 2001 [102]	Bangladesh	BDI>9	3m	161	66	41
			1y	156	65	42
Bayer 2001 [94]	Jordan	DSM IV	3 m	168	42	25
Eriksson 2004 [98]	Sweden	Single question	3 m	13999	1999	14
Fure 2006 [100]	Norway	HAD>6	3-7 d	178	25	14
Kaji 2006 [103]	Japan	HDRS >10	2-5 w	92	23	20
Caeiro 2006 [96]	Portugal	DSM IV	<5 d	178	82	46
Storor 2006[108]	Australia	HDRS>12	Acute phase	61	20	39
Fatoye 2009 [99]	Nigeria	BDI>9	1m-2 y	118	47	40
Beghi 2009 [95]	Italy	DSM IV	Acute phase	82	24	27
S-Jarosz 2010 [107]	Poland	GDS>5	3 m	242	82	34
Raju 2010 [105]	India	HAD>7	1 m – 3 y	162	60	37

Table 2.2 Hospital studies of prevalence of depression after stroke

GHQ: General Health Questionnaire

HAD: Hospital Anxiety and Depression Scale

DSM: Diagnostic and Statistical Manual of Mental Disorders

BDI: Beck Depression Inventory

HDRS: Hamilton Depression Rating Scale,

GDS: Geriatric Depression Scale

Author/Year	Country	Diagnosis	Time since stroke	Assessed (N)	Depressed (n)	Depressed (%)
Daily 1983 [114]	USA	HDRS	7 d	32	5	16
Eastwood 1989 [116]	Canada	GDS	3 w- 6 m	87	47	54
Bacher 1990[111]	Canada	ZDS	Baseline	48	12	25
			6w	43	12	26
			6m	42	10	24
			1y	39	12	31
Morris 1990 [159]	Australia	DSM III	2m	99	32	32
			15 m	56	7	12
Aström 1993 [110]	Sweden	DSM-III	Discharge	76	19	25
			3m	73	23	31
			1y	68	11	16
			2y	57	11	19
			3y	49	14	29
Shima 1994 [129]	Japan	DSM-III R	3m-10y	68	41	60
Diamond 1995 [115]	USA	GDS>10	Admission	14	5	36
			Discharge		4	29
Ng 1995 [128]	Singapore	DSM-III	22d	52	29	55
			Discharge	49	14	29
Angeleri 1997[109]	Italy	BDI>14	2 y	180	62	34
Lincoln 1998 [124]	UK	HAD>10	1 m	84	11	13
Kauhanen 1999 [120]	Finland	DSM-III	3m	101	53	53
			1y	92	39	41
VandeWeg 1999[130]	Netherlands	DSM-III	3-6 w	85	30	35
Jürgensen 1999 [119]	Germany	DSM IV	6 m	77	15	20
Löfgren 1999 [125]	Sweden	DSM IV	3 y	47	18	38
Kellermann 1999 [121]	Hungary	BDI>10	1 w	82	22	27
Langhorne 2000 [123]	UK	Single question	Acute phase	311	50	16
Gillen 2001 [118]	USA	GDS >14	15 d	243	31	13
Mast 2004 [160]	USA	GDS >10	1w	195	71	36
B-Collo 2007 [161]	N.Zealand	BDI>9	3 m	73	13	23
Farner 2010[117]	Norway	MADRS>5	18 d	108	60	56
			13 m	108	52	48
Bergersen 2010 [162]	Norway	HAD>7	3.5 y	162	45	28
Kitisom.2010 [122]	Thailand	GDS >12	3 d	83	47	57

Table 2.3 Rehabilitation studies of prevalence of depression after stroke

HDRS: Hamilton Depression Rating Scale,

GDS: Geriatric Depression Scale

ZDS: Zung Depression Scale

DSM: Diagnostic and Statistical Manual of Mental Disorders

BDI: Beck Depression Inventory

HAD: Hospital Anxiety and Depression Scale

MADRS: Montgomery-Åsberg Depression Rating Scale

No cut off point indicates it was not reported by authors

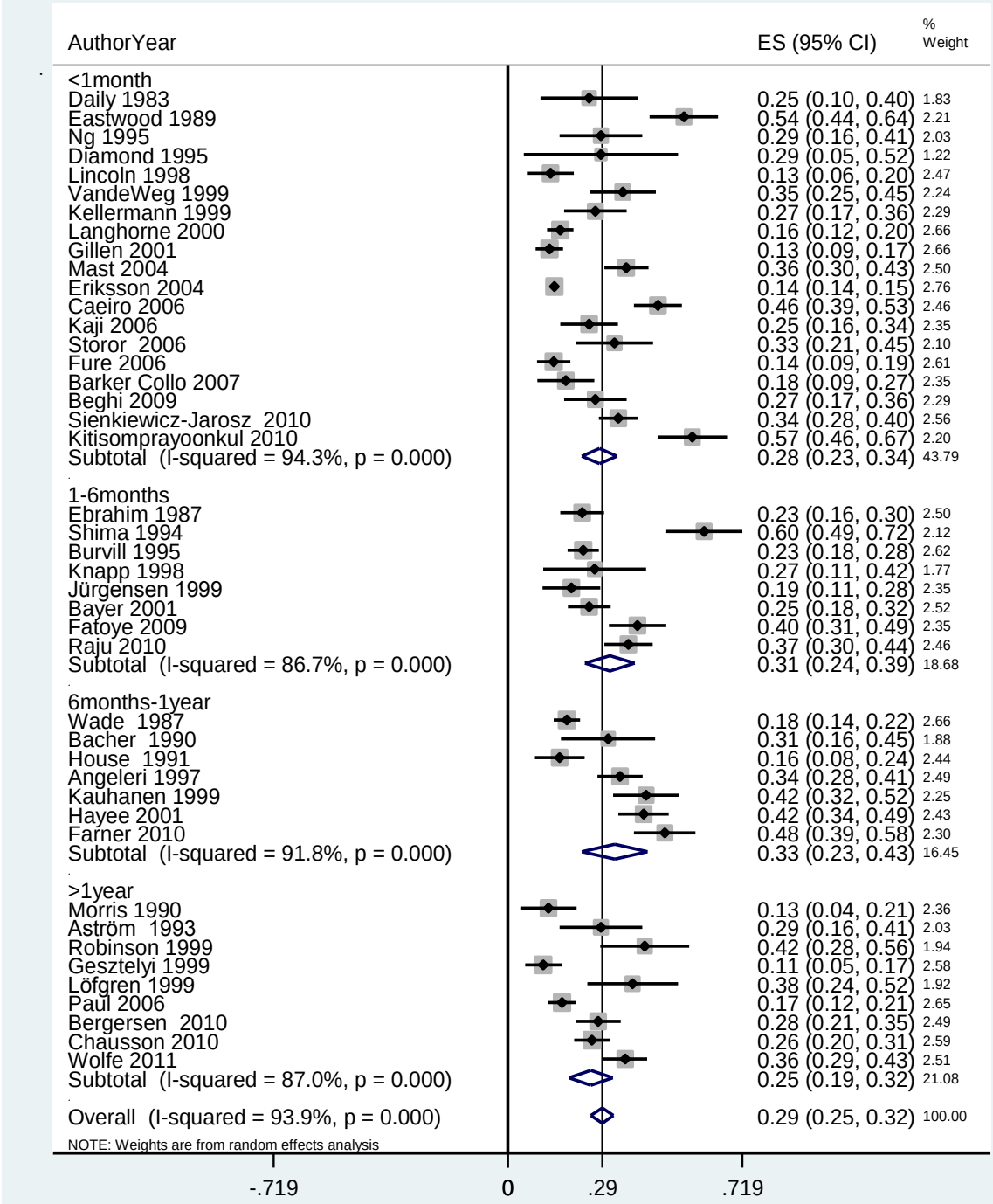


Figure 2.3 Pooled prevalence of depression stratified by length of follow-up

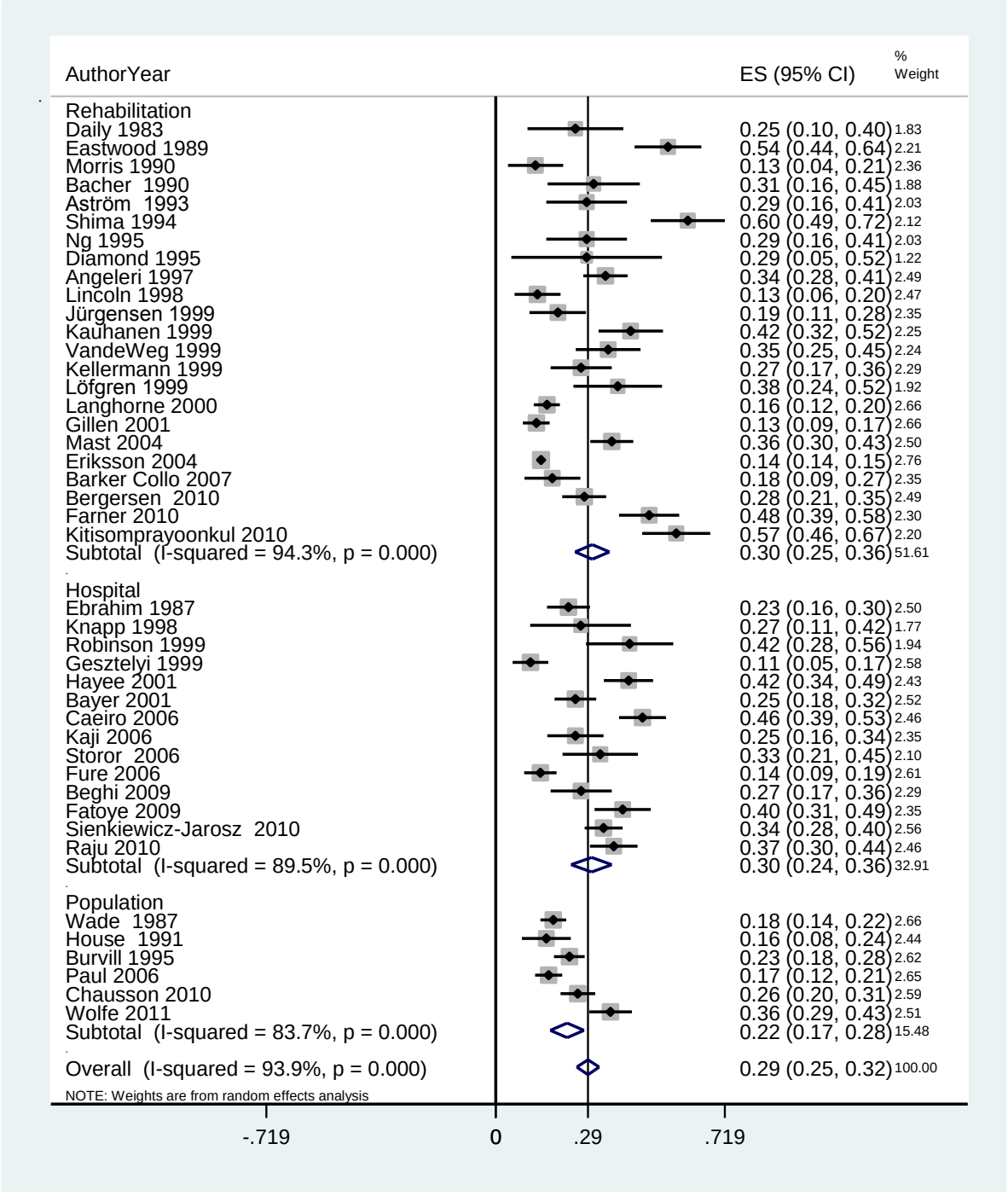


Figure 2.4 Pooled Prevalence of depression stratified by study setting

Four studies reported other measures of natural history of depression after stroke including incidence, cumulative incidence, and duration of depression (Table 2.4).[91 93 110 117 163] Another study reporting measures of natural history of depression afters stroke, and fitting the inclusion criteria, was identified, but it was not included as it reported preliminary results

from this thesis.[163] Incidence in year one was 10% in the only study reporting it. Cumulative incidence ranged from 39 to 48% in two studies with one year of follow-up. Two studies reported that 15 to 57% of patients depressed within three months of stroke had recovered one year after stroke. Three studies reported the proportion of patients depressed in all the assessments, which ranged from 7%, in a study with one year follow-up, to 36% in a study with three years of follow-up. All the longitudinal studies presented a dynamic natural history, with new cases and recovery of depression occurring over time.[91 93 110 117 163]

	Time of the assessments	Cumulative incidence during the follow-up	Proportion of patients recovering at follow-up	Patients depressed in all the assessments	Incident cases (%)
Wade 1987[93]	3 weeks	48%		17%	
	6 months				5% at 6months
	1 year		15% by 1 year		10% at 1 year
House 1991[91]	1 month	39%		7%	
	6 months				
	1 year				
Aström 1993[110]	Discharge			36%	
	3 months				
	1 year		57% by 1 year		
	2 years				
	3 years		36% by 3 years		
Farner 2010[117]	18 days				
	13 months		45% at 13 months		35% at 13 months

Table 2.4 The natural history of depression after stroke

2.4.2 Predictors of depression after stroke

A total of 14,898 patients were assessed in nine studies reporting predictors of depression after stroke fitting the inclusion criteria. The search strategy identified another study reporting predictors of depression after stroke, fitting the inclusion criteria, which was not included in this review as it reports preliminary results of this thesis.[163]

The number of patients assessed for depression in each study ranged from 40 to 13,999. Six of them assessed more than 100 patients[96 98 99 105 117 164] of which only one assessed more than 1,000 patients.[98] The quality assessment of these studies is presented in table 2.5. There were no population based studies. Eight studies were based in hospitals[95 96 98 99 105 108 164 165], and one was a rehabilitation based study.[117] Only three studies assessed the patients more than one year after stroke.[105 117 165]

The assessments for depression were carried out using scales in six studies, DSM criteria in two studies, and a validated question in another one. The time of these assessments ranged from the acute phase to three years after stroke. Six studies stated all the variables included in the models. Six studies did not report that potential confounders had been included in the models. In five studies depression and its predictors had been measured at the same time, making the model less predictive. The ORs and 95% CIs of the associations were not always presented.

	Eriksson 2004[98]	Morrrison 2005[165]	Storor 2006[108]	Caeiro 2006[96]	Beghi 2009[95]	Fatoye 2009[99]	Sagen 2010[164]	Raju 2010[105]	Farner 2010[117]
Study setting	H	H	H	H	H	H	H	H	R
Patients first seen < 7 days of stroke		Yes		Yes					
Time after stroke of Depression assessment	3m	3 y	Acute phase	Acute phase	Acute phase	1month-2 y	Discharge and 4m	1-3y	18d and 13m
Assessed (n)	13999	40	61	178	82	118	150 104	162	108 108
Age and sex included in the model	Yes			Yes	Yes		Yes	Yes	
Variables included in models reported	Yes	Yes		Yes	Yes		Yes	Yes	
Variables included as potential confounders		Yes			Yes		Yes		
Events per variable ratio sufficient	Yes	Yes		Yes				Yes	
Stepwise analysis		Yes		Yes					
Colinearity / Interaction accounted									
Predictors measured before depression	Yes	Yes					Yes		Yes

Table 2.5 Quality of the studies of predictors of depression after stroke

H: Hospital, R: Rehabilitation

The search identified a number of studies reporting predictors of depression after stroke that did not fit the inclusion criteria. These included twenty studies from which patients with haemorrhagic strokes were excluded, [71 100 107 111 122 128 132-134 137 151 154 166-173] another ten studies excluding patients with subarachnoid haemorrhages, [106 110 142 144 146-148 153 174 175] two studies excluding patients with a past history of depression,[122 176] and one study excluding patients with a family history of psychiatric disorders.[148]

Many different predictors were investigated across the nine studies (Table 2.6). Disability was investigated in four studies. One of them reported disability at baseline as a predictor of depression.[163 165] Another two studies reported disability to be associated with depression at follow-up.[98 105] Finally, another study found that disability after stroke was not associated with depression.[164] Past medical history of psychiatric disorders was investigated in different ways in four studies: pre-stroke depression was reported as a predictor of depression after stroke in one study;[96] three studies investigated past medical history of psychiatric disorders[95 99 108] and two of them found a significant association with depression after stroke.[99 108] Cognitive impairment after stroke predicted depression in one study that investigated the association.[99] In this study cognitive impairment had been defined with a score in a scale so no details were given on whether the association was between depression and the executive domain or with other domains of cognitive function. Three studies reported stroke severity not to be associated with depression after stroke.[95 105 165] Another study reported hemiparesis to be associated with depression.[99] Anxiety predicted depression in two studies[164 165] and was associated with depression at follow-up in another one.[105] One study reported an association between living alone after stroke and depression.[98] Age and gender did not predict depression in six out of seven studies. Other potential predictors investigated in fewer number of studies, including co-morbidities, previous history of stroke, education, family type or neuroticism, are also presented in table 2.6

Study/ year	Associated in univariate analysis	Not associated in univariate analysis	Associated in multivariate analysis	Not associated in multivariate analysis
Eriksson 2004[98]	Cognitive impairment on admission	Subtype (Isc/Haem) Stroke unit care Age	Age (<65) Sex (female) PMH of stroke Living alone after stroke Disability after stroke Institutionalised after stroke	Cognitive impairment on admission
Morrison 2005[165]			Low engagement on exercise 1 months after stroke Low satisfaction with treatment 1 month after stroke Handicap in acute phase Anxiety 10-20 d post- stroke	Age Sex Marital status Living arrangements pre-stroke Alcohol consumption pre stroke Laterality PMH of stroke Stroke severity Disability pre-stroke
Storor 2006[108]			Neuroticism PMH of mental disorder	
Caeiro 2006[96]	Sex (female) Hemiparesis in acute phase PMH depression Handicap		PMH of depression	Age Sex Aphasia
Beghi 2009[95]			PMH psychiatric disorder Psychiatric medication use pre-stroke	Age Sex Subtype (Isc/Haem) Location Stroke severity
Fatoye 2009[99]	Education level Cognitive impairment after stroke Paresis after stroke	Age Sex PMH psychiatric illness pre-stroke	Education level (low) Cognitive impairment after stroke Paresis after stroke	
Sagen 2010[164]	Anxiety after stroke		Anxiety after stroke	Age Sex Comorbidities Disability in acute phase
Raju 2010[105]	Disability after stroke Quality of Life Stroke severity	Age Sex	Handicap after stroke Anxiety after stroke Disability after stroke	Age Sex Income Education Family type Stroke severity
Farner 2010[117]			Low activity level pre stroke	

Table 2.6 Predictors of depression after stroke

2.4.3 Associated outcomes of depression after stroke

Five studies reported health outcomes associated with depression after stroke (Table 2.7). A total of 887 patients were assessed for depression in the five studies. Three of them were hospital studies[177-179] and the other two were rehabilitation studies.[117 180] The number of patients assessed for outcomes ranged from 84 to 293. Depression was assessed between the acute phase and three months after stroke. Three studies reported outcomes observed more than a year after stroke.[117 177 178] Only one study described the statistical model used in the analysis.[179]

	Morris 1993[178]	Morris 1993[177]	Kwok 2006[180]	Wulsin 2008[179]	Farner 2010[117]
Setting	Hospital	Hospital	Rehabilitation	Hospital	Rehabilitation
Time of depression assessment	1-3 weeks post-stroke	2 months post-stroke	3 months post-stroke	Acute phase	18 days
N depressed / N assessed	37/91	34/82	94/263	129/343	60/108
Time of outcome assessment	8-11 years	17 months after stroke	1 year	1 year	13 months
N patients with outcome / N patients assessed	48/91	7/84	213 assessed	226 QoL 293 MRS	126 alive (35 institutionalised) 37 dead
Age and sex included in the models	Logistic regression. Model not described	Logistic regression model not described	Multivariate logistic regression model not described	Yes	Logistic regression model not described
Variables in the model reported				Yes	
Potential confounders included		Yes		Yes	
Ratio of events per variable sufficient		No		Yes	
Associations of depression after stroke	Mortality	Mortality	QoL,	Disability QoL	Institutionalization Mortality NOT associated

Table 2.7 Outcomes of depression after stroke

QoL: quality of life. MRS: modified Rankin Scale

The search also identified several studies reporting outcomes of depression after stroke, not fitting the inclusion criteria. These included five papers from which patients with haemorrhagic strokes had been excluded, [143 181-184] two papers that presented estimates for

patients with stroke or transient ischaemic attack together,[185] [186] two studies excluding patients with subarachnoid haemorrhage,[72] [187] and one paper from which patients of non-Chinese ethnicity, pre-stroke handicap and life expectancy under six months were excluded.[188]

Disability was found to be an outcome of depression in one study with OR: 2.68 (1.50-4.78)[179]. Lower quality of life (QoL) was found to be an outcome of depression in the two studies that investigated the association. Both of them used linear regression. One of them reported coefficient for QoL: -0.52 (-0.70- -0.33) [179] and the other one presented separated coefficients for the physical domain of QoL -1.8 (-1.4 - -2.2), psychological domain -2·6 (-2.4- -2.8), social domain -1.2 (-0.8- -1.6) and environmental domain -2.0 (-1.6 - -2.4).[180] Higher mortality was found to be an outcome of depression in two of the three studies that investigated the association. One of them presented strong evidence of association, with OR: 3.4 (1.4-8.9) p=0.007[178]. The other one showed weaker evidence of association, with OR of 8.1 (0.9-72.9) p=0.06[177]

2.5 DISCUSSION

Depression after stroke has been investigated in studies of diverse quality across the world. Some evidence has been provided on its natural history, predictors, and association with health outcomes, although in order to inform effective interventions some areas need further research.

2.5.1 Natural history of depression after stroke

Available studies show that depression has a cumulative incidence up to 48% within a year of stroke with a pooled prevalence of 29% that remained stable in the first ten years after stroke in different study settings. Studies assessing patients more than once suggested that most

patients who have depression after stroke became depressed shortly after the acute event, a significant proportion of them recovered from depression in subsequent assessments, and new cases made the overall prevalence of depression stable. The natural history of depression more than three years after stroke remains unknown. Factors affecting the variation of prevalence of depression reported by individual studies included the different methods used to diagnose depression, source of patient recruitment, and the timing of assessment, together with the different study settings. Without greater methodological uniformity in the studies, it will remain difficult to determine whether heterogeneity in study findings is showing real differences in characteristics of populations or is simply an artefact caused by measurement bias and other errors. These estimates may still be inaccurate because of potential under-reporting of abnormal mood, especially in patients with communication impairment[60], and the possibility of over reporting depression by using screening questionnaires.

A previous systematic review published in 2005 reported that the prevalence of depression after stroke was stable across studies conducted at different time points and in different settings.[60] This systematic review includes fourteen new studies with six studies conducted in Europe, three studies conducted in Oceania, three in Asia, one in America and one in Africa. However, there is no significant difference between the prevalence observed in this study and the one previously reported.[60] Our results show the great stability of the prevalence of depression across studies conducted in different time points. The prevalence of depression was stable, despite the fact that aetiological factors of depression may be different at different time points. Stroke survivors in the first weeks were coping with the consequences of the direct neurological damage, the experience of a life-threatening event, and the initial stages of rehabilitation. In the medium to long term, survivors were more likely to be adjusting to disability and changes in social and financial circumstances.[79]

Only one population based study recruited controls to allow estimates of the relative risks of depression after stroke.[91] They reported that the prevalence of depression in stroke survivors was twice that in controls, although this difference was only significant at the six months follow-up assessment. Another robust examination of the relative risk of depression in stroke survivors was undertaken in The Framingham Study, a prospective, observational, community-based study that enrolled middle-aged subjects who have been followed-up biennially since the middle of the past century. They reported that significantly more stroke survivors were depressed than controls matched for age and gender.[189]

2.5.2 Predictors of depression after stroke

Disability after stroke and history of depression pre-stroke are the predictors of depression after stroke most consistently reported with three studies presenting a significant association. Other predictors were cognitive impairment, stroke severity, lack of social or family support, and anxiety.

Depression pre-stroke and anxiety were not reported as predictors of depression after stroke in a previous review.[62] Risk factors for depression, connected or not to stroke (e.g.: genetic factors), may explain the strong association between depression before and after stroke.

The associations between stroke severity and depression were not completely consistent. The association between stroke severity and disability may be a possible explanation for the inconsistent association between severity and depression observed in this study. Whether the association between stroke severity and depression is independent or partly, or completely explained by the association between severity and disability remains unknown.

The association observed in this chapter between depression and impaired cognition is complex as both can be cause or effect of each other and they also have common risk factors.

Patients with cognitive impairment deserve special attention in any case as their risk of depression may be increased and they may be unable to report their symptoms.

No association was found between depression and other variables representing neurological damage, such as stroke subtype, lesion location or laterality of stroke. A previous systematic review of depression and stroke lesion location concluded that there was no evidence suggesting that the risk of depression after stroke is affected by the location of the brain lesion.[190] The importance of neurological damage on depression after stroke appears to be limited to cognitive impairment and stroke severity.

Other medical conditions did not predict depression after stroke. Despite the well established association between chronic illness and depression,[191-193] the results of this review suggest that depression after stroke is mostly associated with the experience and consequences of stroke itself.

The negative impact that social isolation has on general health may play a role in its association with depression after stroke.[194] [195] Other variables connected to personal, professional and social life, such as education level and family structure, have been investigated in a little number of studies of good quality. Therefore, there is still insufficient evidence about their possible association with depression.

Age and gender were found not to be predictors of depression in most studies investigating these associations. In general population the prevalence of depression is higher in women.[14] However, our observations suggest that after stroke prevalence of depression becomes similar in men and women.

2.5.3 Associated outcomes of depression after stroke

The evidence on the outcomes of depression after stroke is still limited, with only five studies of unselected stroke patients investigating this area. The very brief description of the statistical models reported in most studies makes it difficult to assess the validity of the results. Low quality of life was an outcome identified repeated times.[177 179] Another study of good quality identified in the electronic search observed an association between depression and lower quality of life but patients with TIAs had been included together with patients with stroke and that made the results difficult to interpret.[185] Mortality was observed to be an outcome of depression in two studies.[177 179] The electronic search identified other studies including two of good quality, from which patients with haemorrhagic strokes had been excluded, observing an association between depression and mortality. The interpretation of these results was made with caution as the difference in the populations with the studies of unselected stroke patients was noted.[181 187] In an attempt to investigate the causal associations between depression and its outcomes, only studies were the outcomes had been assessed after depression were included in this review. A previous systematic review reported many possible outcomes of depression after stroke, including higher disability rates, higher mortality, and poor involvement in rehabilitation, longer hospital stay and poor cognitive function. However in that review, they included studies where depression and its potential outcomes had been assessed at the same time. This makes difficult to know whether depression is actually cause or consequence of the variable investigated as potential outcome.[63] We found weak evidence, or none at all, supporting that other variables apart from disability, lower quality of life and mortality may be outcomes of depression in stroke patients.

2.5.4 Strengths and limitations of this review

The comprehensive search, and critical assessment, of studies of unselected stroke patients conducted in this review allows estimation of the natural history predictors and outcomes of depression after stroke obtained over a large number of patients across the world. The search strategy used in this chapter was comprehensive in order to include all the relevant studies.[83] The specific design of the studies may not be part of their title, and it may not be one of the key words indexed, therefore the search strategy was made extensive, very sensitive and not that specific, to include as many relevant papers as possible. It is acknowledged that no search strategy can guarantee the inclusion of all relevant literature therefore some papers may have been missed. Although the guidelines for reporting meta-analyses of observational studies were used as a reference, the data was extracted only by the author of this thesis and this can be another source of inaccuracy in the results. Even so, all the data were checked for accuracy on multiple occasions and all analyses were conducted repeated times and checked by a senior statistician.

The methods for research synthesis proposed by the Cochrane collaboration and the MOOSE statement,[82 83] used in this chapter, are considered to be at the highest standard.[196] Medical journals invariably require compliance with these guidelines.[196] However, these methods have limitations as well and the application of formal meta-analytic methods to observational studies has been debated.[197] One reason for this has been that potential biases in the original studies make the calculation of a single summary estimate of effect of exposure potentially misleading. Acknowledging this potential error the systematic review presented in this chapter reports individual data from each study as well as pooled estimates. It has also been reported that diversity of study designs and populations in epidemiology makes the interpretation of simple summaries problematic, at best.[197] In order to deal with this limitation

the inclusion criteria was defined aiming to remove most of the methodological and clinical heterogeneity. Some of the studies identified in the electronic search, not fitting the inclusion criteria, are cited in the results section, the discussion, and also in the following chapters as their results were considered of interest. Despite these challenges, the methods used in this chapter for meta-analyses of observational studies are one of the few methods for reliable synthesis of previous research[68] The rationale for using these methods was therefore to improve the reporting of these analyses so that readers could understand exactly what was done in a given analysis, who did it, and why was it done. Methodological and interpretational concerns make the clear and thorough reporting of meta-analyses of observational studies absolutely essential.[82]

This systematic review aimed to identify studies reporting three types of results: natural history estimates, predictors, and outcomes of depression after stroke. This introduced some complexity when assessing and selecting studies after the automatic search. However, this approach allowed producing an integrated piece of research, providing the current evidence on the epidemiology of depression after stroke required to raise the questions to be answered in this thesis. All searched studies were observational, and their design had little variation. In fact, many identified papers presented more than one type of results e.g.: prevalence and predictors, or prevalence and outcomes. These advantages were also considered when designing the search strategy.

The diversity of the methods used across studies may have an effect on the external validity of each individual one. In this review, this effect was minimized by conducting a comprehensive search, and the categorization of studies by setting and length of follow-up. The summary of results of individual studies provides estimates that can be used in clinical practice and in the development of further research.

The funnel plot was asymmetrical (Figure 2.5.) Different reasons for such asymmetry were considered.[83] Papers on depression after stroke have been published regularly since the eighties so bias caused by delayed publication, “time-line” or “pipeline” bias, was thought to be unlikely. The search strategy did not have limitations for language so the possibility of language bias was not considered to be relevant. While the search strategy included checking references from previous systematic reviews, most results came from an electronic search of studies indexed in four databases. Therefore, citation bias was also considered to have little or no impact on the funnel plot asymmetry. As described in the methods section, the publication of results from the same study in different papers, without referencing a common data source, was addressed by checking all papers carefully. After this assessment, if doubts about the similarities of different papers remained, the authors were contacted. However, it is possible that some "multiple publications" may have been miscoded or missed altogether. The lack of cross-referencing of data from some cohorts has served to mislead the research community, specifically in the area of depression after stroke.[60] Another explanation for the asymmetry of the funnel plot is that some authors obtaining low figures of prevalence may have chosen not to report them, or editors of medical literature may have rejected to publish these manuscripts. The low prevalence of depression may make it look less relevant and therefore studies with such results may not have been published. All these reasons may explain the bias in the literature that this funnel is showing.

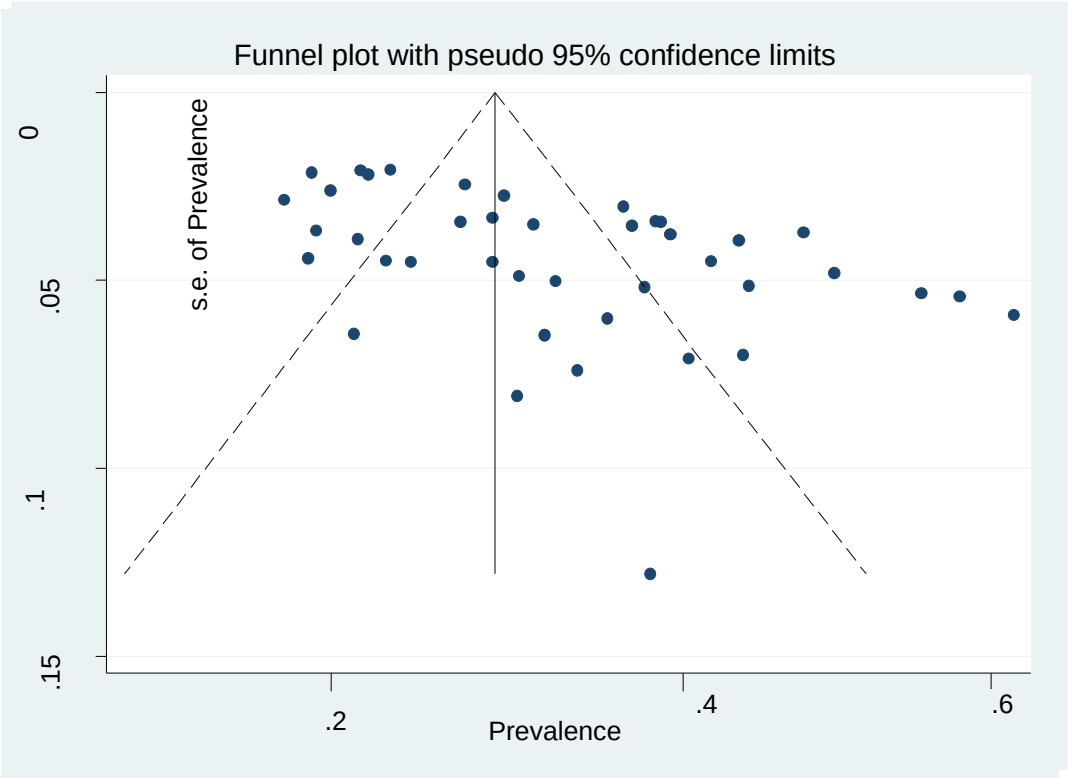


Figure 2.5 Funnel plot of studies included

2.5.5 Implications for clinical practice

Clinicians patients and carers should be aware that depression after stroke is a frequent clinical problem that may make the overall prognosis of stroke poorer. The natural history of depression after stroke, which appears to be dynamic, should also be considered acknowledging that patients depressed at one point may remain depressed in the following years, and also the significant risk of depression in patients who are not depressed shortly after stroke

Particular attention should be paid to patients with disability and previous history of depression, as the risk of depression after stroke seems to be higher in these groups. Patients with cognitive impairment, severe strokes, anxiety, and living in isolation also deserve special attention.

2.5.6 Implications for further research

The available studies provide insufficient evidence to understand the burden of depression in the long term after stroke and to inform effective interventions for it.[78 79] The long term natural history, predictors, and outcomes of depression after stroke need further research. A detailed description of the natural history of depression after stroke, including its prevalence, incidence, cumulative incidence in the long term, time after stroke of depression onset, duration of the episodes, and recurrence rate, would provide strong evidence on when and for how long interventions may be required. The identification of predictors of depression after stroke would help clinicians to identify patients at a highest risk of this problem, in which interventions should focus. Finally, in order to understand the impact of depression in stroke patients, the association between depression after stroke and other health outcomes, including mortality, disability and stroke recurrence, should be investigated further.

Population based studies, providing the least biased sampling frame, with large sample size and repeated assessments of patients for long follow-up, are needed to describe the natural history of depression after stroke, its predictors and outcomes in the long term.

The lack of a formal study design may substantially impair the interpretation of the results, and selective reporting of results can be detrimental. The ethical duty of researchers includes reporting findings with accuracy, completeness and transparency, and in sufficient detail to allow the scientific community to consider them adequately, assess their strengths and weaknesses and make fair comparisons. The adherence of future studies to standard validated methods accepted for prognostic models in stroke cohorts,[26 88 198] will help in the interpretation of their results. Evidence produced in these studies should be robust and easily applicable in health policy, clinical practice and research.

2.5.7 Questions to be addressed by this thesis:

This thesis aims to provide evidence in areas, identified in the systematic review, where it is poor or lacking by addressing the following questions that are still unanswered:

I. Frequency of depression after stroke in the long term:

- What is the incidence of depression in the long terms after stroke?
- What is the cumulative incidence of depression after stroke?
- What is the prevalence of depression in the long term after stroke?

II. Natural history of depression after stroke

- When after stroke do patients become depressed?
- How long do episodes of depression last?
- What proportion of patients has recurrent depression?

III. Predictors and associations

- What social and clinical variables, present at baseline or at follow-up, are associated with depression in the long term after stroke?

IV. Outcomes:

- Is depression after stroke associated with higher rates of mortality, stroke recurrence, disability, cognitive impairment, or low QoL?

CHAPTER 3: THE SOUTH LONDON STROKE REGISTER (SLSR) FRAMEWORK FOR THIS THESIS

3.1 ABSTRACT

Background: population based registers provide the least biased information of the epidemiology of a specific disease and its long term outcomes.

Objective: To describe the methods used in the SLSR and present the rationale to use its data on this thesis.

Methods: The SLSR is a prospective ongoing population-based stroke register set up in January 1995, recording all first-ever strokes in patients of all age groups from a defined multi-ethnic area of South London. Stroke is defined according to WHO criteria. Standardized criteria are applied for ensuring completeness of cases ascertainment. Multiple overlapping sources are used to register patients including daily visits to acute wards in the hospitals serving the study area, weekly checks of brain imaging, and reviews of bereavement officers and of bed manager records.

Trained field workers collect all data prospectively within 48 hours of stroke. Data collected on the initial assessment includes: age, gender, ethnicity, stroke severity measures and stroke subtype. Three months after stroke, one year after stroke and annually thereafter, patients are followed up. Assessments carried out at follow-up include measures of depression (Hospital Anxiety and Depression Scale), cognitive impairment (Abbreviated Memory Test or Mini Mental Exam), Disability (Barthel Index) and Quality of life (SF 12 and SF 36)

Results: 4022 patients were registered in the SLSR between 1995 and 2009. Registration of strokes occurring in the area has been estimated to be 88% complete.

Conclusion: the data from these patients constitutes a unique framework to estimate the natural history, predictors and associated outcomes of depression up to 15 years after stroke, objectives of this thesis.

3.2 INTRODUCTION

The objectives of this chapter are:

- To describe the characteristics and methodology of the South London Stroke Register, database used in this thesis.

- To outline the rationale for using a population based register to investigate depression after stroke

3.3 IMPORTANCE OF A POPULATION BASED STROKE REGISTER

The development of disease management programmes, as a way to improve the health care provided to patients with chronic illnesses, is an international priority.[80 199] Population based, disease specific, registers have received special attention.[80] The strong evidence that is obtained from them can make an important contribution to the improvement of health services.[199] Measurements of the overall health status of the populations that quantify the impact of disease are important for clinicians, researchers and policy makers. These measurements can include prevalence, incidence, and mortality rates.

However, to measure the impact of illness, indicators that fully reflect the effect of disease on society such as long term outcomes of the disease must also be included.[80] Most hospital based studies assessing outcomes from chronic disabling diseases are restricted to selected patients, such as those admitted to hospital or those referred to rehabilitation. Major disadvantages of these studies are various forms of selection bias which may lead to the wrong estimation of the real clinical course and prognosis of the disease. The variable case-mix of hospital based studies often limits the degree to which results can be applied to other groups of patients. An important limitation, in epidemiological terms, of hospital or rehabilitation based studies is the lack of reliable denominator and therefore the impossibility

to obtain good quality frequency measurements, such as disease incidence or prevalence. A comprehensive picture of the disease outcome requires the inclusion of patients not admitted to the hospital, including very severe or very mild cases; hence, the concept of a population based disease register (PDR) ascertaining all cases of a condition. To achieve complete case ascertainment the PDR has to be truly population based. Some stroke registers are not so and they have hospital cases only, assuming that no stroke patients remain in the community.

3.4 THE SLSR DEFINITION

Solomon and colleagues[200] described a PDR as: A database of identifiable persons within a population containing a clearly defined set of health and demographic data collected for a specific public health purpose. This definition is most appropriate for the SLSR which is a prospective longitudinal population based stroke register, established on 1st January 1995, in a multi-ethnic, inner city population of 271,817. Data are collected for first in a lifetime stroke patients of all ages. Wherever possible, follow-up data for subjects in the SLSR are collected at three months after stroke, one year after stroke and annually thereafter. The SLSR contains a defined set of demographic and health data with clear purpose of estimating the impact of stroke by providing broader measures of stroke outcome.

3.5 CRITERIA FOR REGISTER

The SLSR is based on standardised criteria: [201 202]

<u>Core criteria for a comparable study of stroke incidence:</u>

- Standard definitions:

  - WHO definition

  - First ever in a lifetime stroke

- Standard methods:

  - Complete community based case ascertainment based on multiple overlapping sources

  - Prospective study design, ideally with “hot pursuit of cases”

  -Large, well defined stable population

  -Reliable method for estimating denominator

- Standard data presentation

  -Whole years of data

  - Not >5 years of data aggregated together

  - Men and women presented separately

  - Includes ages up to and above 85 years

  - Standard mid-decade age bands used in publications

  - Unpublished five year age bands available for the comparison with other studies

  - Presentation of 95% confidence intervals around incidence rates

3.6 DEFINITION OF STROKE

The SLSR uses the World Health Organisation definition of stroke: Rapidly developing clinical signs of focal or global neurological deficit lasting more than 24 hours or leading to death, with no apparent cause other than of a vascular origin.[1]

Patients with focal neurological signs recovering within 24 hours, haemorrhages originated in cerebral tumours or, cerebrovascular events secondary to trauma, are not included in the SLSR.

3.7 POPULATION COVERED BY THE SLSR

Cases of first ever stroke are identified in an area defined by postcodes of Lambeth and Southwark, South London. The total population was 271,817 according to the 2001 census data from the Office for National statistics. This populations consists of 63% white, 28% black (15% African-Caribbean, 9% Black African and 2% Black mixed) and 9% of other ethnic groups.

3.8 DATA COLLECTION

Multiple overlapping sources of notification of stroke are used to ascertain stroke cases. These sources are exploited by "hot" pursuit of cases to achieve a high level of case-ascertainment e.g.: the sources are actively pursued by the register staff to detect any stroke cases rather than passively wait for their notification from various sources. This concept is essential for any population based stroke register aiming to improve accurate estimates of various stroke outcomes. Hospital surveillance of admissions for stroke includes three teaching hospitals within (Guy's, St. Thomas' and King's) and others outside the study area. Community surveillance of stroke includes patients under the care of all general practitioners (GP) within and on the borders of the study area.

These sources of notification include:

1- Telephone contact is made with all wards at St Thomas', Guy's and King's hospitals twice a week. St George's, Chelsea & Westminster and Queen Square hospitals are also contacted

once a week. The register staff also visit some wards personally, especially wards where stroke patients are most likely to be admitted, such as the stroke units.

2- Consultants and junior doctors particularly in neurology, elderly care medicine and general medicine are encouraged to notify any strokes that they may see in their clinical practice, both as in-patients and outpatients.

3- Records of Head CTs or MRIs are screened two to three times a week Patients with results suggesting a stroke are investigated further for possible registration.

4- Records in bereavement offices are regularly checked and the notes of all cases, where stroke is mentioned on the death certificate, are then examined to detect stroke cases.

5- Death and Coroner's records: Death certificates from the Health Authority serving the SLSR population and post-mortem records from the local coroner's office are also searched every three months.

6- GP surgeries notify the register of any strokes by telephone, electronic mail or by post. GPs are made aware of the register and kept informed of progress and any changes.

7- Therapists from the local community hospitals (Whittington, Pulross and Lambeth Community Care Centre) notify the register of cases. They are also sent regular newsletters to update them on the project.

8- To ascertain the strokes that occur out of area, the Lambeth, Southwark and Lewisham Health Authority is contacted every six months for details of billing from other Authorities for their treatment.

9- An updated list is sent every six months to the Office for National Statistics (ONS) of all patients who were alive who were known to be deceased but for whom there was no death record. They inform the register every two to three months of any patients that have died.

10- Miscellaneous: Notification by relatives or informal carers of stroke patients.

A capture-recapture analysis conducted with the data on incident strokes registered in the SLSR in 1995 and 1996 concluded that 88% of the strokes occurring in the study area were being registered.[203] NICE guidelines on management of acute stroke recommend, since their first edition in 2000, that all stroke patients should be assessed at the hospital.[76] Implementation of these guidelines would have led to a lower number of strokes patients being managed exclusively in the community, with an increasing number of them receiving at least part of their health care at the hospital where they are easier to register. This may have increased the proportion of incident strokes occurring in the study area that are registered in the SLSR.

3.9 INFORMATION COLLECTED ON INITAL ASSESSMENT

Initial assessments of stroke patients are performed by SLSR field workers within 72 hours of onset of stroke symptoms whenever possible. The patients are assessed in hospital if admitted, but for non-hospitalised stroke patients they are seen at home or in an outpatient stroke clinic. Data are collected by acquiring information from patients, their relatives, friends, carers, medical records, and where necessary, their general practitioner. Thus, it is possible to obtain pre stroke information such as pre-morbid disability even in those patients who are unable to communicate at initial assessments. Registration criteria and data collected are checked with the patient's general practitioner and medical records for any discrepancies. Any difficult cases are discussed with the senior doctors involved with the register and a consensus reached before registration.

The information collected on initial assessment relevant for this thesis is described below. A sample of the form used to collect data on first assessment is presented in appendix 2.

3.9.1 Socio-demographic details:

Socio-demographic data includes, age at the time of the stroke (and date of birth), sex, ethnicity, social class, work situation and living conditions prior to stroke. Ethnicity is stratified into three groups (1991 census question): white, black (Caribbean, African and mixed), and others including Asian, Indian, Pakistani, Bangladeshi, Chinese and others. Social class categories are grouped into non manual (I, II non manual), manual (III manual, IV, V) and economically inactive (student, unemployed, unable to work because of disability, being a carer or retirement). Only paid work before stroke is considered. Working situation is stratified in patients working full time or part time, unable to work due to disability, retired and others. Living conditions prior to stroke is stratified in living alone, living with carer, and living in an institution.

3.9.2 Stroke severity measures

Clinical state at the time of maximal impairment (within 72 hours) includes: level of consciousness according to the Glasgow Coma Scale (3-15) stratified into severe (3-8), moderate (9-12) and mild (13-15), levels of consciousness impairment;[76] dysphagia assessed by the water swallowing test;[204] visual fields defects assessed by the patient confrontation test; visuo-spatial neglect (inattention) assessed by the confrontation test; dysphasia assessed by clinical examinations to see if there is a deficit in comprehension, expression, naming, reading or writing out of command; dysarthria; motor weakness or paralysis on the affected side; sensory loss; cerebellar symptoms such as limb ataxia; urinary incontinence defined as loss of bladder control or catheterisation within 48 hours of assessment.

The SLSR has collected data on the National Institute of Health Stroke Score (NIHSS)[205] since 2001. This scale provides a very reliable and intuitive value for stroke severity.[206] However, when the SLSR started in 1995, stroke severity was registered from clinical findings, such as GCS and other acute impairments. Having complete NIHSS data from 1995 would have been ideal especially in the analysis of outcomes of depression after stroke. However, the stroke severity variables included in the models used in this thesis were chosen for their clinical relevance, and their prognostic value, which was observed in two previous studies.[207 208]

Cognitive level is assessed with the Mini Mental Test Exam (MMSE)[209] or the Abbreviated Memory Test (AMT).[210] MMSE score under 24 or AMT 0-7 are considered cognitive impairment. The psychometric properties of the MMSE have been reviewed and its strengths and limitations have been discussed.[209] Items measuring language have been judged to be relatively easy but not very useful in identifying mild language deficits. MMSE scores can also be affected by age, education, and cultural background. It shows higher levels of sensitivity for moderate-to-severe cognitive impairment. Overall reliability and construct validity were judged to be satisfactory by the reviewers.[209]

The AMT performance has also been investigated, showing to be sensitivity and specificity of 91% and 75% when scores under eight are used to identify abnormal cognitive function.[210]

Disability is categorised, according to Barthel Index (BI),[211] scores of 0-14 are categorised as severe disability, 15-19 moderate disability, and 20 independent. While the sensitivity to change of the BI has been reported to be limited in severe disability (ceiling effect), evidence still suggests that it is a valid measure of activities of daily living. The BI was chosen for the analyses conducted in this thesis, after observing its strengths and weaknesses, as it is widely

used in clinical settings and in up to 40% of stroke trials. It also has excellent test-re-test (kappa w = 0.98) and inter-rater reliability (kappa w = 0.88).[211 212]

3.9.3 Co-morbidity

A medical history of hypertension, myocardial infarction, diabetes mellitus, atrial fibrillation, disability (BI), past medical history of depression or pharmacological treatment at the time of the stroke is identified through hospital and primary care records. When considering the use of these variables for this thesis it was acknowledged that past medical history may not always be accurately or systematically recorded in medical notes. However, most of the data of past medical history used in this thesis is relevant for the management of stroke, and this probably improve its completeness and accuracy in medical records.

Validated questions are used to assess smoking and alcohol use. Patients are categorised as current smoker, ex-smoker or never smoker. If applicable, the time they have been smokers for, and the amount of tobacco smoked per day, are also recorded. Data on alcohol use is collected as number of units consumed in an average week. Alcohol intake and smoking habit were included in the analyses presented in this thesis. However, it was noted that data on alcohol and smoking were sensitive and therefore the information given by patients could not be entirely reliable.[213]

3.9.4 Classification of stroke subtypes

The stroke subtype is categorised as infarct, primary intracranial haemorrhage, subarachnoid haemorrhage and undefined.

3.10 FOLLOW-UP ASSESSMENT

Stroke patients registered in the SLSR are followed up at three months after their stroke, at one year, and annually thereafter. Follow-up is by postal questionnaire, or interview with the patient and/or carer, depending on the capacity of patient to respond to the questionnaire. Such capacity is judged by the patient, the next of kin, or the field worker in a previous follow-up assessment. Patients unable to complete the follow-up questionnaire, and those not returning them by post, are telephoned to arrange face to face interviews, or have another follow-up questionnaire posted. Proxy assessments by carers are conducted mainly for the objective portion of these assessments. The follow-up questionnaires are standardised into an easy to read format to enable patients to fill in the questionnaire themselves and all the forms for each time point are identical so that longitudinal comparisons can be made. While the repeated annual measure of the same items in the long term is a strength of the SLSR data, it is acknowledged that some variables may not be stable over time and the assessments one year apart may not fully reflect all the real changes that are actually happening. Patients who cannot be assessed at one time point, remain registered and are contacted again for subsequent follow-up assessments. A sample form used to collect data at follow-up is presented in appendix three.

At follow-up patients are assessed for depression and anxiety, using the Hospital Anxiety and Depression scale (HAD).[214] HAD was first presented in 1983 by AS Zigmond and RP Snaith as a tool to identify possible cases of depression and anxiety among patients in non-psychiatric hospital clinics. It was conceived as a brief practical tool for physicians and surgeons, who are usually aware of the emotional components of their patients' illnesses but, have little time to deal with them. It is therefore a short scale and it is limited to the two mental health problems that Zigmond and Snaith considered to be the most common in non

psychiatric hospital practice: anxiety and depression.[214] It has two questionnaires, one for anxiety and another one for depression. The seven items composing the depression subscale were largely based on the anhedonic state since the authors of the scale considered that this provided the most useful information for the clinician. The seven items composing the anxiety subscale were chosen from previous research from the authors into the psychic manifestations of anxiety.[215] Items in both scales exclude symptoms which might equally arise from somatic as from mental disease such as insomnia, anergia, fatigue and pessimism about the future. While the deletion of somatic items from the questionnaires may avoid overdiagnosing depression in the medical setting, this practice risks underdiagnosing patients who present mostly with somatic symptoms.[19 20] Symptoms relating to severe mental disorder (such as suicidal preoccupation or phobic limitation) were also excluded; although such symptoms are common in patients attending psychiatric clinics they were considered by Zigmond and Snaith to be less common in patients attending other hospital clinics and therefore less likely to be useful.[214]

The degree of psychological distress is continuously distributed in the population[19 20] therefore questions related to "how much?" were considered by the developers or the scale to be more relevant than those related to "is it present?" Scales related to mood disorders make a better reflection of the reality if they are presented in terms of score ranges. The HAD scale is presented with these score ranges in both subscales. Each item on the questionnaire is scored from cero to three and this means that a person can score between zero and 21 for either anxiety or depression. Two of the seven questions on the HAD depression subscale "I feel as if I am slowed down" and "I have lost interest in my appearance" present negative effects of depression while the other five present statements such as "I feel cheerful" which the patient with depression has to score negatively. The scale is brief and well accepted by patients. It can be completed in two to six minutes and scored in approximately one minute.[216] Its

easiness makes of HAD an ideal instrument to be used in large clinical epidemiological studies.

The designs of the HAD scale attempts to overcome response bias in the scale by alternating the order of responses. Therefore, to one item the first response indicates maximum severity and to another item the first response indicates minimum severity. The choice of four responses to each item was adopted in order to prevent the patient from opting for a middle grade to all the items.[214] The use of HAD may still introduce some response bias since the non-responders, the intellectually impaired, the socially or educationally disadvantaged, the uncooperative may be those whose psychological problems may be more in need of detection.

Since the HAD scale was published it has been used many times in studies assessing depression and anxiety amongst patients with a great variety of non-psychiatric conditions. In 2007 it was reported to be the third most commonly used self-administered screening instrument.[217] The first assessment of the HAD's validity was carried out by its developers, who reported for the depression subscale 1% false positives and 1% false negatives.[214] A systematic review of the properties of HAD published in 2002 reported optimum performance of the scale when scores above seven were used to identify anxiety and depression (Cronbach's alpha> 0.80; sensitivity and specificity ranging from 0.70 to 0.90).[218] The positive and negative predictive value of HAD when assessing stroke patients for depression, with cut-off point of seven, have been reported to be 0.61 and 0.90 respectively.[219] Finally, a more recent systematic review on HAD's validity was published in 2010. Twenty five studies, published between 1988 and 2005 were included. In 15 on those HAD had been compared with the DSM diagnostic criteria. The other ten studies compared HAD with other scales including the Primary Care Evaluation of Mental Disorders and the Geriatric Mental State interview. The conclusions of this review supported the use of cut-off

point of seven to identify depression and reported a sensitivity of 0.82, specificity of 0.74, positive likelihood ratio 3.17 (2.09-4.08) and negative likelihood ratio 0.24 (0.17-0.34).[217]

The two factor structure of HAD has been debated.[220] The results of one systematic review support the two-factor structure of HAD. In most studies, where empirically based exploratory factor analyses were used, HAD revealed two relatively independent dimensions of anxiety and depression closely identical to the anxiety and depression subscales.[218] Another review reported that there is sufficient evidence that both scales differ in a clinically meaningful way. The correlation between HAD(D) and HADS(A) is mostly due to the simultaneous presence of anxiety and depression and to a lesser extent to inadequacies of the instrument.[216] The stability of the results obtained with HAD was considered as some of the symptoms of depression may have a short duration. However, HAD(D) has been reported to have test-re-test reliability in two weeks r=0.85, two to four weeks 0.76, and over six weeks 0.70.[216]

The performance of HAD in the SLSR population was also studied carefully. HAD has been validated in stroke patients It shows a good performance both when it is used in a face to face interview and when it is self-administered.[219 221] One of the systematic reviews observing the properties of HAD also reported that it has the same properties when applied to samples from the general population, general practice, and psychiatric patients.[218]

Another point for discussion is that small changes in the clinical state of patients, when the HAD scale is used to define a binary variable, can result in patients being identified as depressed or not. As presented above, the cut-off point used in this thesis was reported in three systematic reviews to be the one that gives the scale optimum performance.[216-218] In addition, the clinical interpretation of analyses of continues variables is more complex. HAD has been validated against criteria from the Diagnostic and Statistical Manual of Mental

Disorders, that also gives a binary classification of patients.[217 222] In clinical medicine many health problems are routinely identified by scores above a cut-off point of a specific variable. E.g.: Hypertension or diabetes when blood pressure, or fasting glucose, are above a certain threshold.

In summary, it was accepted that HAD does not provide results as accurate as the clinical assessment of depression. However, after reading all the reviews on its performance and considering its strengths and weaknesses, HAD was judged to be an appropriate tool to make repeated assessments of depression in a large cohort of long term stroke survivors.[216-218 221 219]

HAD was routinely collected between 1997 and 2010. Patients registered in 1995 (n=299) and 1996 (n=350) didn't have their first HAD assessment until 1997. Data on HAD was therefore not included from these patients in the respective estimates for early rates of anxiety and depression. Despite its good performance HAD is not a diagnostic scale but a tool that indicates risk of depression. Some authors would argue that HAD only measures risk of depression or symptoms of depression. However, the term "depression" will be used in this thesis for succinctness in patients with scores above seven. HAD cannot be answered by proxy so all information was collected directly from patients. Although patients with some degree of cognitive or communication impairment can respond to HAD, no data could be collected from patients with severe cognitive or communication impairment that the fieldworker, or the patient's next of kin in case of a postal questionnaire, judged would give invalid responses.

Depression and Anxiety Scale

Items relating to Depression

1. I feel as if I am slowed down:
☐**nearly all the time** ☐**very often** ☐**sometimes** ☐**not at all**

2. I still enjoy the things I used to:
☐**definitely as much** ☐**not quite as much** ☐**only a little** ☐**hardly at all**

3. I have lost interest in my appearance:
☐**definitely** ☐**I don't take as much care as I should**
☐**I may not take as much care as I should** ☐**I take just as much care as ever**

4. I can laugh and see the funny side of things:
☐**as much as I always could** ☐**definitely not so much now**
☐**not quite so much now** ☐**not at all**

5. I look forward with enjoyment to things:
☐**as much as I ever did** ☐**definitely less than I used to**
☐**rather less than I used to** ☐**hardly at all**

6. I feel cheerful:
☐**not at all** ☐**not often** ☐**sometimes** ☐**most of the time**

7. I can enjoy a good book or radio or TV programme:
☐**often** ☐**sometimes** ☐**not often** ☐**very seldom**

Items relating to Anxiety

1. I feel tense or 'wound up':
☐**most of the time** ☐**a lot of the time** ☐**occasionally** ☐ **not at all**

2. I get a sort of frightened feeling like butterflies in my stomach:
☐**not at all** ☐**occasionally** ☐**quite often** ☐**very often**

3. I get a sort of frightened feeling as if something awful is about to happen:
☐**very definitely and quite badly** ☐**yes, but not too badly**
☐**a little, but it doesn't worry me** ☐**not at all**

4. Worrying thoughts go through my mind:
☐**a great deal of the time** ☐**a lot of the time** ☐**from time to time** ☐**only occasionally**

5. I feel restless as if I have to be on the move:
☐**very much indeed** ☐**quite a lot** ☐**not very much** ☐**not at all**

6. I get sudden feelings of panic:
☐**very often indeed** ☐**quite often** ☐**not very often** ☐**not at all**

7. I can sit at ease and feel relaxed:
☐**definitely** ☐**usually** ☐**not often** ☐**not at all**

Figure 3.1 Hospital Anxiety and Depression Scale (HAD)

Other outcomes assessed at follow-up include the following ones:

- Residential status, categorised as living alone, with someone or in an institution.

- Employment categorised as paid work full time or part time, unable to work due to disability, retired and others.

- Cognitive function, measured with the Mini Mental Test Exam (MMSE)[209] between 1995 and 2000 and the Abbreviated Memory Test (AMT)[210] between 2001 and 2009.

- Disability using the Barthel index (BI).[211]

- Handicap, using the Frenchay activity index (FAI) Stratified as inactive 0-15, moderate inactivity 16-30, or active 31-45.[223] The metric properties of the FAI have been studied in stroke patients. It has been reported that the FAI could be improved by creating two subscale scores: domestic and outdoors activities.[223] Male patients of some cultures may score lower than women as some items are about activities traditionally conducted by women. However, the reliability of unweighted scores has shown to be high, with a range of Cronbach's alpha-coefficients, 0.78 to 0.87. The construct validity was supported by meaningful correlations between the FAI and scores on the BI and Sickness Impact Profile. Principal-components analysis indicated that the FAI showed two traits: instrumental disability and some aspects of handicap. Completion of the questionnaire was noted to be easy, taking only a few minutes. The FAI has been considered to be a suitable instrument both for patients' assessments and descriptive studies.[223]

- Social networks are also assessed. Physical illness commonly increases patient's needs for support of various kinds.[20] Illness may also interfere the individual's capacity to acquire and maintain social networks.[19 20] One indication of the possible social origin of depression in

stroke survivors is the high correlations between their depression and that of their carers.[24] However, there has been more agreement in literature regarding what is social support and its potential association with health outcomes than regarding its measurement.[19 20] Social support was measured by the SLSR by asking questions: Do you see as much of your relatives as you would like? (Yes/No or don't have any). Do you see as much of your friends as you would like? (Yes/No or don't have any). These questions regarding social isolation that were included in the SLSR follow-up assessments have not been validated. Since they ask about contact with relatives and friends they have a quantitative component aiming to see if these relationships exist. However, from the way the questions are phrased (… as much as you would like?), they also ask about the quality of these relationships. Therefore, they cover the quantitative and qualitative elements of social support that have been considered to be relevant among patients with physical conditions at risk of depression.[19 20] Social isolation is currently a matter of research, approached both in observational and interventional studies, as it has strong association with health outcomes.[224 225] Ideally, validated measures of social isolation should be used that allow generalisation and an adequate interpretation of results.

- Quality of life (QoL) was assessed with the SF-36[226] between 1995 and the 29th of February 1999 and SF-12[227] between the 1st of March 1999 and 31st August 2010. Two domains of QoL were observed mental domain and physical domain. Scores collated from the scales ranged from 0 to 100 with high score representing better QoL.[226 227] The properties of both scales have been reviewed. One study concluded that the SF-36 seems acceptable to patients, internally consistent, and a valid measure of the health status of a wide range of patients.[228] Test-re-test reliability of both scales is over 70%. Empirical evidence and factor analysis also support the internal validity and the factor structure of both the SF-12 and SF-36.[229]

Data on deaths is collected by the SLSR follow-up team or from the Office of National Statistics (ONS). Finally Death certificates from the Health Authority serving the SLSR population and post-mortem records from the local coroner's office are also searched every three months.

The same overlapping sources used by the SLSR to identify first ever strokes are used to identify recurrent strokes.

3.11 ETHICAL APPROVAL OF THE SLSR

The ethics committees of Guy's and St Thomas' Hospital NHS Foundation Trust, King's College Hospital Foundation, National Hospital for Nervous Diseases, Queen's Square Hospital, St George's Hospital and Westminster Hospital approved the study.

Before being registered patients or their relatives gave written informed consent. Sample consent and assent forms are presented in appendix 4

3.12 ADVANTAGES OF THE SLSR

There are several strengths that make the SLSR an ideal and unique data-set for addressing the objectives proposed in this thesis:

1- The SLSR provides a unique data-set of unbiased community based first-in a life time strokes of all subtypes in all ages in a multi-ethnic, inner city population. This was useful in accurately quantifying the association between stroke and depression, and the association between depression after stroke and other health outcomes. The SLSR overcomes the limitations of hospital based studies that do not include patients managed exclusively in the community (mostly very severe or very mild cases).

2- The SLSR has follow-up data at several time-points, over a 15 years period, which makes possible to conduct longitudinal comparisons of stroke outcomes over time.

3- The SLSR has a wide collection of standardised, widely used stroke outcomes, across the domains of impairment, disability, handicap and health related quality of life, all of which provided a more holistic outcome of stroke.

4- The SLSR has all the characteristics essential for an ideal population-based register:

a) A clear and concise implementation plan for the register

b) Adequate documentation on who would manage the register, inclusion and exclusion criteria, definition of data sources, collection, editing, and entry procedures, protocols for matching to other data sources, data processing procedures, analyses that will be routinely conducted, confidentiality guidelines and access procedures. These procedures ensure that all staff works to the same objectives, identifying appropriate cases and documenting the relevant data.

c) “Hot pursuit” of cases to maximise case ascertainment

d) Effective multiple sources of notification systems to ensure that maximum number of cases in the study area are registers

e) Commitment from registry staff and local data providers including hospital consultants and general practitioners

f) Efficient methods for data collection and processing procedures

g) Adequate procedures to safeguard confidentiality of information in the register

h) Quality control procedures to ensure completeness, validity and timelines which determine the quality of data. Completeness is the proportion of cases on the target population that appear on the register. Validity in the percentage of cases in the register with a given characteristic, e.g.: sex or stroke subtype, which truly has this attribute. Timeliness may be important in those registers that identify persons needing critical and rapid services. The SLSR has principles that are likely to ensure quality control including having a manual with explicit quality control procedures and with regular audit of these procedures, and senior member providing feedback loop to inform data handlers of errors by reviewing each data set before it is entered onto the computer and identifying data items that are missing, out of range or inconsistent.

3.13 LIMITATIONS OF THE SLSR

There are limitations and practical difficulties with the SLSR that must be acknowledged. Limitations specific to the depression assessments are discussed in the following chapters. General limitations of the SLSR are presented below:

1- Despite the "hot pursuit" of cases and multiple overlapping sources of notification, there are some cases that may not have been identified. Cases difficult to identify include those who had a strokes while away from the study area, those who had mild stroke and were not referred to the register or to any of the hospitals for specialist assessment or investigations.

2- Although the population denominator data derived from census data from the Office for National Statistics, population growth, mobility and cross boundary effects are difficult to estimate and may influence results derived from the SLSR.

3- The estimation of clinical outcomes using scales introduces some limitations. The strengths and weaknesses of each specific scale have been discussed in the methods section of this chapter. It should be noted that all scales have good performance and they allowed assessing a very large number of patients during a long follow-up, which would have been unfeasible otherwise. The imperfect measurement of variables introduced by the scales is a limitation associated with the epidemiological nature of this study. It is accepted that clinical observations are more accurate than epidemiological ones as part of this accuracy is lost when observing populations.[208 213]

4- As expected in a cohort of older people followed for a long time there is a natural attrition of the cohort due to mortality during the years. As mortality reduces the number of observations the statistical power drops leading to more imprecise estimates at the end of the follow-up. Mortality, and its association with depression, is one of the variables of interest of the analyses. However most of this research focuses on outcomes that can only be present in survivors. In order to correct some statistical analyses in which the power was low and the confidence intervals wide, the arcsine correction was used.[230] This method is described in the chapters where it is used.

5- Survival of stroke patients has improved in the recent decades so attrition is higher amongst patients registered shortly after the SLSR started in 1995. However, the long term estimates come precisely from these groups of patients, as in 2010, when the dataset for this thesis was defined, only patients registered before 2000 had been followed up for over ten years. Future studies using SLSR datasets may find higher rates of long term stroke survivors.

6- Any clinical research involving thousands of patients, followed up for over ten years, will invariably have missing data due to various reasons including late registrations, loss to follow-up, or refusal by the patient or their carer.

A great effort was made by the SLSR field work team to minimise the proportion of missing data. Measures to obtain maximum completeness included visits to patients with disability to help them complete the follow-up questionnaires, consideration of cultural background of the patients when arranging the follow-up interviews, reminders on the post or over the telephone for patients not filling in follow-up questionnaires, possibility of having telephone follow-up interviews, and meetings of the SLSR team with groups of patients to discuss their involvement in research.

The residual missing data was handled in the analysis of natural history using inverse probability weighting. In the analysis of predictors missing data was handled using multiple imputation. In the analysis of outcomes of depression missing data was handled using sensitivity analysis. Although inverse probability weighting and multiple imputation are becoming more widely used, they are methods still under development. All the references describing them had been published after 2008.[231] [232] [233] [234] No previous studies of depression after stroke approaching missing data with these methods were identified in the literature review. Acquiring the skills to apply these methods required specific training and in many cases discussions with the statisticians developing them. The management of missing data is discussed further in chapters four to six.

7- It is particularly difficult to obtain complete data-sets from subjects who have language or cognitive disorders as a consequence of their stroke. Assessments of these subjects by proxy provide some useful information. However, the measurement of the main outcomes

of this study, depression, by proxy gives specially limited results as discussed further in chapters four to six.

8- Given the length of the SLSR (currently in its 15th year), one practical difficulty is maintaining continuity of data collection at all times. Such difficulties include securing funding to maintain appropriate numbers of register staff and adequate overlap during changeover of staff. However, a regularly updated manual can circumvent this limitation to some extent.

3.14 CONCLUSION

The SLSR constitutes a unique dataset from which to estimate the natural history, predictors and associated health outcomes of depression in the long term after stroke.

All the data described and analysed in the thesis have been obtained from the SLSR. Baseline data from patients registered between the 1st January 1995 and the 31st December 2009 (N at registration=4022), and follow-up data from these patients, collected between the 1st April 1995 (first 3 months follow-up assessments) and the 31st august 2010, were used.

3.15 PERSONAL CONTRIBUTION, EXPERIENCE AND PROFESSIONAL DEVELOPMENT

Most of the data for this thesis had been collected previously, between 1995 and 2009. I was involved in prospective data collection from 2009 therefore I collected some of the data for this thesis while working in the SLSR as a clinical research fellow (2009-2013). During this time I gained invaluable experience in research methodology and clinical stroke medicine. I personally conducted all the analyses presented in this thesis including the ones regarding missing data.

All this contributed considerably to my own personal and professional development. Specific areas of training and experience included: comprehensive literature searches, study design, epidemiology field work, clinical training in acute stroke medicine, advanced statistical methods, scientific and academic writing, presentation of my work in national and international meetings, and teaching clinical epidemiology to medical students.

CHAPTER 4: THE NATURAL HISTORY OF DEPRESSION UP TO 15 YEARS AFTER STROKE.

4.1 ABSTRACT

Background: Evidence on the natural history of depression after stroke is still insufficient to inform effective interventions to treat this problem.

Objective: To estimate the incidence, prevalence, cumulative incidence, time of onset, duration, and recurrence rate of depression up to 15 years after stroke.

Methods: Data from patients registered in the South London Stroke Register between 1995 and 2009 were used (n at registration=4022). Depression was assessed in all patients with the Hospital Anxiety and depression scale (scores>7 =depression) three months after stroke, one year after stroke and annually thereafter up to 15 years after stroke. Inverse probability weighting was used to calculate the estimates accounting for missing data. Weighted and crude estimates are presented.

Results: The prevalence of depression was around 30% and remained stable in the 15 years following a stroke, with incidence ranging from 7 to 21% and cumulative incidence of 55%. Most episodes of depression started shortly after stroke, with 33% of them starting in the three months following a stroke and no new episodes from year ten onwards. 50% of the patients with depression at three months had recovered one year after stroke. The majority of the patients presenting depression in the long term had had episodes of the depression shortly after stroke.

Conclusion: Depression affects more than half of the stroke patients with episodes starting shortly after stroke, having a short duration and a high recurrence rate, leaving the overall

prevalence stable. This makes the natural history of depression after stroke very dynamic. The evidence provided in this chapter may be considered in the design of interventions.

The description of the natural history of depression up to 15 years after stroke was presented as an oral presentation in the 2011 European Stroke Conference and has been published as an original research paper in Stroke. (See appendix one).

4.2 INTRODUCTION

The literature review presented in chapter two showed that depression after stroke has been investigated in numerous studies across the world. However, most of the studies had short follow-up and small sample size, with patients being assessed for depression only once. The prevalence of depression shortly after stroke was the estimate more frequently reported. Other estimates of natural history of depression after stroke, such as the incidence, cumulative incidence, the time after stroke of depression onset, the duration of depression, and the recurrence rates were reported by a very little number of studies or not reported at all.

Although the available studies of depression after stroke provide valuable evidence, it is still insufficient to understand the nature of the problem. With the available evidence it is not possible to develop effective interventions for depression after stroke. A Cochrane systematic review reported the limited effect of interventions to treat depression after stroke.[79] Authors of the review questioned whether interventions had been started at the right time after stroke, and whether they had been given for an adequate length of time to obtain maximal sustained response.

This chapter aims to provide evidence on the natural history of depression after stroke, in the areas where there is insufficient or it is lacking. The following questions are addressed:

- What is the prevalence of depression up to 15 years after stroke?

- What is the incidence of depression up to 15 years after stroke?

- What is the cumulative incidence of depression up to 15 years after stroke?

- When after stroke do patients become depressed?

- How long do episodes of depression last?

- What proportion of patients has recurrent depression?

With the evidence reported in this chapter clinicians patients and carers will have a better understanding of the risk and the possible course of depression after stroke. It will also be possible to observe how different is the natural history of depression after stroke from the observed in studies of depression in general population. This will lead to a better understanding of depression in general.

A description of the long term natural history of depression after stroke will help in the optimisation of available interventions. It will be possible to know when should the interventions be delivered and for how long. Depression after stroke has been mostly described a few months after the acute event allowing for interventions to be developed during the acute phase of stroke. During this phase hospital clinicians lead the delivery of interventions leaving general practitioners a secondary role. However, it is plausible that depression may affect patients in the long term. The description of the natural history of depression after stroke might help to inform interventions long time after stroke that may also need the involvement of primary care clinicians and other community workers.

4.3 METHODS

Data analysed in this chapter have been obtained from the SLSR. Baseline data from patients registered between 1st January 1995 and 31st December 2009 (N at registration=4022), and follow-up data from these patients, collected between the 1st April 1995 (first 3 months follow-up assessments) and the 31st August 2010, were used. The methodology of the SLSR has been described in chapter three and is summarised below.

First-in-a-lifetime stroke patients, living in a defined area of South London were registered. Sociodemographic data collected at baseline included age, gender, and ethnicity. Stroke severity measures data collected at baseline included Glasgow coma scale score, categorized as severe (3–8), moderate (9–12), and mild (13–15) levels of impairment, urinary incontinence, and paresis. Activities of daily living were assessed seven days after stroke using the Barthel Index. Patients were followed up three months after stroke, one year after stroke and annually thereafter. At follow-up, patients were assessed for depression using the Hospital Anxiety and Depression (HAD) scale. Scores >7 were classified as depression. HAD scores were routinely collected between 1997 and 2006. Patients registered in 1995 (n=300) and 1996 (n=349) did not have their first HAD scale assessment until 1997. Data on HAD scale therefore were not included from these patients in the respective estimates for early rates of depression. HAD scale cannot be answered by proxy, so all information was collected directly from patients. Although patients with some degree of cognitive or communication impairment can respond to the HAD scale, no data could be collected from patients with severe cognitive or communication impairment that the fieldworker judged would give invalid responses.

Estimates and confidence intervals of prevalence, incidence, cumulative incidence, time of onset, duration and recurrence of depression from three months to 15 years after stroke were calculated.

4.3.1 Prevalence

Prevalence of depression was defined as the proportion of patients found to be depressed at each follow-up assessment, from three months to 15 years after stroke.

The prevalence of depression was calculated amongst survivors assessed at each time point. The numerator of the proportion would be patients who have depression at each time point and the denominator all patients assessed at each time point of the 15 years of follow-up.

For example the prevalence in year two would be the proportion of patients with depression expressed as a percentage of all patients assessed in year two.

4.3.2 Incidence

Incidence of depression from one to 15 years after stroke was defined as the proportion of patients not depressed in each follow-up assessment found to be depressed in the subsequent one.

The incidence of depression was calculated amongst patients not depressed at each assessment, who survive and where assessed in the subsequent follow-up.

For example incidence in year five would be the proportion of patients not depressed in year four becoming depressed in year five expressed as a percentage of all patients not depressed in year four surviving and being assessed in year five.

Incidence of depression three months after stroke was not calculated as there were no depression assessments before that point, therefore at three months incident and not incident cases were indistinguishable.

4.3.3 Cumulative incidence

Cumulative incidence of depression after stroke was defined as the proportion of patients found to be depressed at any of the assessments during the 15 years of follow-up.

The cumulative incidence of depression was calculated amongst patients assessed for depression at any time point.

The proportion of patients depressed at any of the assessments over 15 years was calculated and expressed as a percentage of all assessed patients during that time.

4.3.4 Time of onset of depression after stroke

The proportion of patients who become depressed for the first time at each assessment between three months and 15 years after stroke was calculated amongst patients with complete follow-up until each time point. The numerator of the proportion would be patients with complete follow-up becoming depressed for the first time at each time point and the denominator would be all patents with complete follow-up until each time point.

For example the proportion of patients with onset of depression at year three would be patients with complete follow-up until year three becoming depressed for the first time in year three expressed as a percentage of all patients with complete follow-up until year three.

4.3.5 Duration of episodes of depression after stroke

Two different calculations were undertaken:

First, the number of subsequent episodes of depression, throughout the follow-up time, was observed. A categorical variable was defined to assess the number of episodes of depression. Duration of depression could only be calculated amongst episodes that had complete data from onset to recovery. For example episodes lasting three years were those in which the patient was not depressed in one assessment, then depressed in three consecutive assessments and then not depressed in the last one.

Episodes with long duration required continuous follow-up for longer period than short episodes. Therefore, episodes with long duration were much more likely to have missing data and it could be misleading to present this category as a proportion. Therefore only absolute numbers are presented.

Second, as a large proportion of patients have their first symptoms of depression three months after stroke, the number of subsequent episodes of depression starting at three months was observed until patient recovered (was found not to be depressed). The proportion of patients depressed at three months who recover at each time point was calculated amongst patients with complete follow-up until each time point. For example patients depressed at three months recovering at year five would be patients with depression at three months who have a complete follow-up to year five, who reported to have recovered in year five, expressed as a percentage of all patients with depression at three months and complete follow-up until year five.

4.3.6 Recurrence of depression after stroke

Recurrence of depression was defined as a new case of depression in a patient who had been depressed at a previous assessment.

The proportion of recurrences was calculated amongst patients who had three or more follow-up assessments. The proportion of incident cases in which a previous episode of depression had been reported was calculated.

For example, the proportion of recurrent cases in year seven is calculated as incident cases in year seven with a previous episode of depression expressed as a percentage of all incident cases at year seven with previous depression assessments.

4.3.7 Missing data management

Sociodemographic and clinical characteristics of survivors completing and not completing HAD were compared using chi-squared test, as these variables were categorical.

As a first step all estimates of prevalence, incidence, cumulative incidence, time of onset, duration and recurrence of depression were obtained only from patients with complete data, that is complete case (CC) analysis. This analysis is based on the assumption that missing data were missing completely at random (MCAR). With MCAR it is assumed that the distribution of depression would be the same for subjects who were followed up or lost to follow-up. The probability of an observation being missing does not depend on observed or unobserved measurements and individuals with complete data are assumed to represent a random sample of the population of individuals, with the similar distribution of covariates.[231] [235] Under MCAR, the analysis of only those patients with complete data is assumed to give valid results.

However, this assumption may not always be appropriate. Estimates obtained from CC analysis may be biased if the excluded individuals are systematically different from those included.[231] Therefore, in a second step the assumption that missing data were not MCAR but missing at random (MAR) was considered. MAR is a term used in longitudinal data analysis meaning that all individuals are not equally likely to be observed. The probability of being observed depends only on other observed variables.[232] For example the probability of having complete data in year three of the follow-up depends on the stroke severity recorded at baseline.

A third possibility is to assume that missing data may be missing not at random (MNAR). This is the case when the probability of being observed depends on unobserved variables. For example the probability of having complete data in year three depends on the unobserved

disability in year three. However, the statistical methods needed to handle missing data under the MNAR assumption are computationally intensive and not routinely included in statistical software so they are not commonly applied.[232] The MAR assumption was considered the most appropriate one to handle missing data in this thesis.

Several methods are available to handle missing data using the MAR assumption. Inverse probability weighting (IPW) and Multiple Imputation (MI) were the two methods initially considered for these analyses. Both methods require modelling the possibility of the data being complete. MI is generally a more complex method. It is more difficult to build a model that explains the variability of completeness with MI than with IPW.[231] Therefore IPW was chosen. Using IPW cases are weighted by the inverse of their probability of being a complete case. To weight the probability of being complete a variable of completeness was created for each estimate. For example, prevalence of depression at three months 1=observed, 0=missing. A logistic regression model was built to identify predictors of completeness. Variables included in the models were those considered to be associated with completeness: age, sex, ethnicity, stroke severity measures (GCS, incontinence and paresis) and disability at baseline. Only variables collected at baseline were introduced in these models. The inverse of the probability of being a complete case was calculated and applied to individuals with available data. The predicted probability for each participant represents the probability for participants with similar characteristics of responding to the HAD questionnaire. For example, a predicted probability of response for a patient of 0.5 suggests that there will be an identical participants who will not respond. The participant who responds will be given a weight of 2, (1 divided by 0.5) to represent themselves as well as an identical hypothetical participant that didn't respond. Finally estimates were calculated on weighted data. Un-weighted and weighted estimates are presented.

IPW was not used to estimate rate of recurrences as the number of patients available each year was too low, between one and 68, to allow for a stable model of completeness to be built.[88]

Some estimates, particularly those obtained with small number of patients towards the end of the follow-up, had confidence intervals with values over one or under cero. In these cases the arcsine correction was used.[230] When this correction was used IPW was not possible, therefore only crude estimates were reported.

4.4 RESULTS

Between 1995 and 2009 the SLSR registered 4,022 patients. When the follow-up period finished in August 2010, the follow-up time for survivors ranged from three months to 15 years. The number of patients registered in each period, assessed for depression or lost to follow-up, at each time point, is presented in figure 4.1. Sociodemographic description of the cohort at each follow-up is presented in table 4.1. There were little differences between sociodemographic characteristics of patients who were and those who were not assessed for depression (Table 4.2). Up to ten years after stroke those who had had more sever strokes were less likely to be assessed. (Table 4.3).

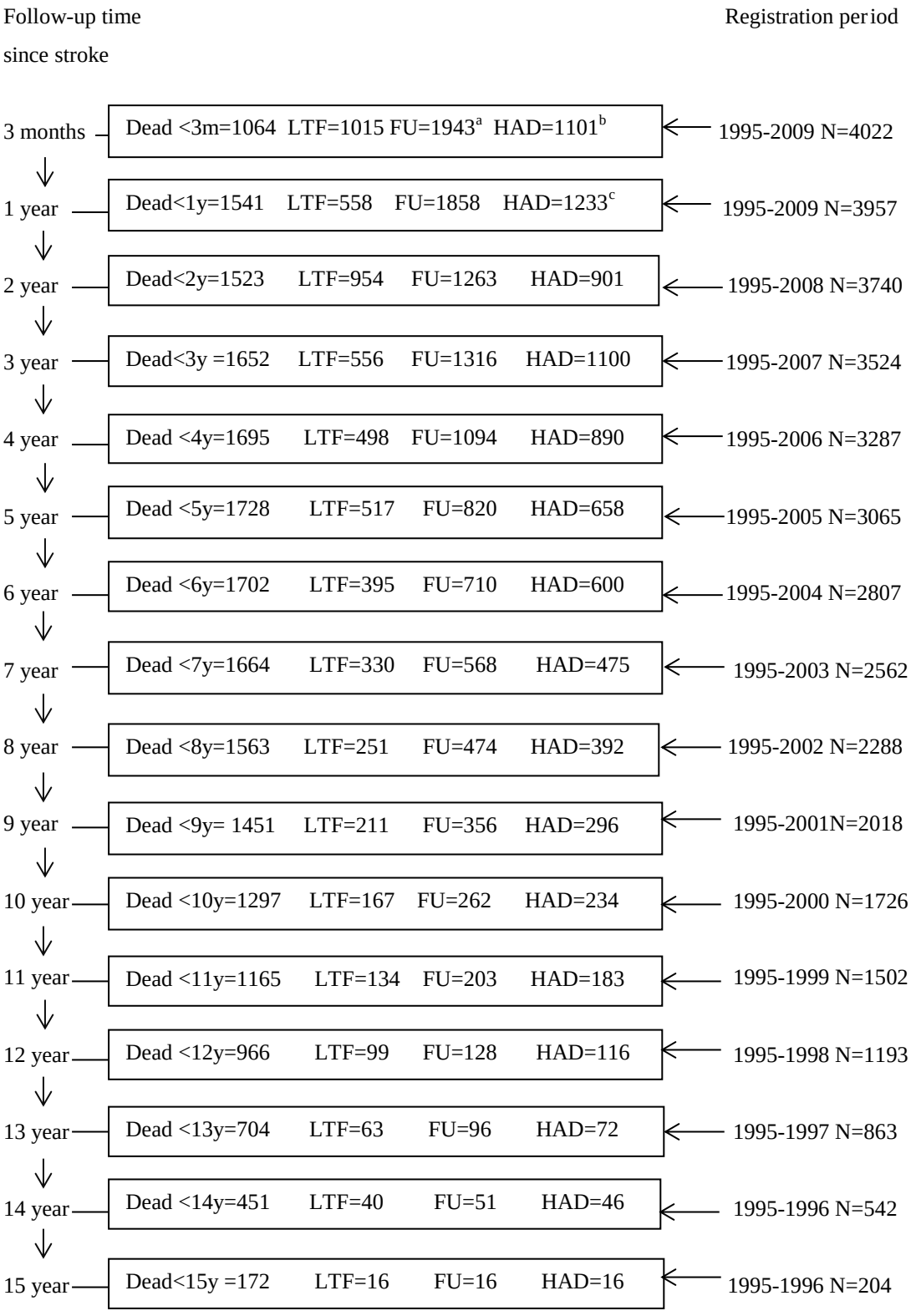


Figure 4.1 Number of participants included in the analysis at each follow-up time point

N= number of patients registered.

HAD=number of patients completing the depression scale.

FU= Number of patients followed up at each time point.

LTF=Number of patients lost to follow-up at each time point.

a- Some patients who were followed up could not be assessed with HAD due to cognitive or communication impairment.

b- The 649 patients registered in 1995 and 1996 were not assessed for depression at this point as HAD was routinely collected from 1997.

c- The 299 patients registered in 1995 were not assessed for depression at this time point as HAD was routinely collected from 1997.

	Age n(%)		Gender n(%)		Ethnicity n(%)			
	<65	>64	Male	Female	White	Black	Other	Unknown
3m	393(35.7)	708(64.3)	595(54.0)	506(46.0)	773(70.2)	247(22.4)	67(6.1)	14(1.3)
1y	481(39.0)	752(61.0)	683(55.4)	550(44.6)	865(70.1)	276(22.4)	76(6.2)	16(1.3)
2y	367(40.7)	534(59.3)	496(55.0)	405(44.9)	594(65.9)	233(25.9)	64(7.1)	10(1.1)
3y	469(42.6)	631(57.4)	631(57.4)	469(42.6)	765(69.5)	254(23.1)	66(6.0)	15(1.4)
4y	409(46.0)	481(54.0)	484(54.4)	406(45.6)	602(67.6)	217(24.4)	59(6.6)	12(1.3)
5y	330(50.1)	328(49.8)	384(58.4)	274(41.6)	444(67.5)	155(23.6)	51(7.7)	8(1.2)
6y	296(49.3)	304(50.7)	337(56.2)	263(43.8)	412(68.7)	144(24.0)	39(6.5)	5(0.8)
7y	241(50.7)	234(49.3)	273(57.5)	202(42.5)	323(68.0)	118(24.8)	28(5.9)	6(1.3)
8y	219(55.9)	173(44.1)	240(61.2)	152(38.8)	249(63.5)	114(29.1)	25(6.4)	4(1.0)
9y	18161.1)	115(38.8)	174(58.8)	122(41.2)	199(67.2)	75(25.3)	19(6.4)	3(1.0)
10y	146(62.4)	88(37.6)	137(58.5)	97(41.4)	159(67.9)	58(24.8)	17(7.3)	(0)
11y	101(55.2)	82(44.8)	112(61.2)	71(38.8)	126(68.8)	43(23.5)	12(6.6)	2(1.1)
12y	70(60.3)	46(39.7)	74(63.8)	42(36.2)	82(70.7)	26(22.4)	8(6.9)	(0)
13y	48(66.7)	24(33.3)	46(63.9)	26(36.1)	49(68.1)	20(27.8)	3(4.2)	(0)
14y	29(63.0)	17(37.0)	28(60.9)	18(39.1)	30(65.2)	14(30.4)	1(2.2)	1(2.2)
15y	4(80.0)	7(43.7)	7(43.7)	9(56.2)	10(62.5)	4(25.0)	1(6.2)	1(6.2)

Table 4.1 Sociodemographic characteristics of the survivors assessed at each time point

(Age and gender had no missing data)

	HAD completed / HAD not completed [d]			
	Age>65(%)	Female gender (%)	White ethnicity (%)	Black ethnicity (%)
3m	64.3/64.9	46.0/47.4	71.1/70.1	22.7/23.2
1y	61.0/65.3*	44.6/46.2	71.1/68.3	22.7/24.8
2y	59.3/59.5	44.9/44.1	66.7/69.3	26.1/24.0
3y	57.4/55.6	42.6/45.2	70.5/62.8**	23.4/27.7**
4y	54.0/55.4	45.6/40.7	68.6/62.6*	24.7/28.2*
5y	49.8/55.3*	41.6/43.8	68.3/64.5	23.8/27.3
6y	50.7/50.7	43.8/42.4	69.2/61.5*	24.2/29.4*
7y	49.3/48.2	42.5/40.7	68.9/59.9*	25.2/31.7*
8y	44.1/47.2	38.8/44.2	64.2/63.8	29.4/28.0
9y	38.8/46.9	41.2/39.8	67.9/60.3	25.6/30.7
10y	37.6/44.4	41.4/41.8	67.9/58.1	24.8/33.5
11y	44.8/35.7	38.8/42.2	69.6/61.4	23.8/30.7
12y	39.7/35.1	36.2/43.2	70.7/56.0*	22.4/38.5*
13y	33.3/40.2	36.1/44.8	68.1/61.2	27.8/30.6
14y	37.0/39.1	39.1/37.0	66.7/63.0	31.1/30.4
15y	43.7/50	56.2/25.0	66.7/56.2	26.7/37.5

Table 4.2 Comparison of sociodemographic characteristics of the survivors assessed, and not assessed, with the HAD at each time point

d- Survivors who did not complete the HAD were either lost to follow-up or unable complete the HAD due to cognitive or communication impairment.

* $p<0.05$

** $p<0.01$

	HAD completed / HAD not completed [d]			
	GCS>12 (%)	Urine Incontinence (%)	Paresis (%)	Barthel Index=20 (%)
3m	90.0/84.3 **	26.7/36.0 **	73.2/75.1	32.5/29.1 **
1y	90.7/84.1 **	25.0/34.8 **	69.8/77.7 **	37.8/26.3 **
2y	89.5/86.8 *	22.8/31.4 **	69.3/75.5 *	41.2/28.7 **
3y	88.7/86.5	24.7/31.8 **	71.0/74.0	37.0/32.7 *
4y	90.6/86.3 *	23.4/30.9 **	69.2/74.6 *	40.6/33.7 **
5y	89.7/88.4	21.3/28.7 **	66.9/74.6 **	41.9/36.9
6y	90.6/85.8	18.1/30.7 **	67.8/74.3 *	44.4/34.3 **
7y	90.2/86.1	20.0/27.4 *	66.1/74.4 **	43.1/36.3
8y	90.1/85.7	20.0/27.2 *	67.1/71.7	42.1/38.0
9y	89.4/87.1	17.0/28.8 **	66.4/72.4	46.4/32.4 **
10y	87.9/87.8	19.8/27.8	66.5/72.6	44.3/32.9 *
11y	88.9/85.2	20.2/32.4 *	66.3/70.7	41.0/28.2
12y	85.1/86.2	25.7/28.7	72.2/71.8	38.2/29.9
13y	81.7/88.4	29.6/28.2	81.9/74.4	25.7/35.8
14y	87.0/91.3	26.1/21.7	82.6/80.4	31.8/35.6
15y	93.7/93.7	18.7/25.0	81.2/81.2	40.0/56.2

Table 4.3 Comparison of the stroke clinical characteristics of survivors assessed, and not assessed, with HAD at each time point

d- Survivors who did not complete the HAD were either lost to follow-up or unable complete the HAD due to cognitive or communication impairment.

* $p<0.05$

** $p<0.01$

4.4.1 What is the prevalence of depression up to 15 years after stroke?

The prevalence of depression was stable at around 30% throughout the follow-up period. Weighted and crude estimates were very similar, with overlapping confidence intervals at all time points. Crude and weighted estimates of prevalence of depression up to 15 years after stroke are presented in table 4.4. Figure 4.2 shows graphic representation of crude estimates and confidence intervals.

Follow-up	Patients assessed	Patients depressed	Prevalence (95%CI)	Weighted prevalence (95%CI)
3months	1101	361	32.8 (30.0-35.6)	33.2 (30.0-36.4)
1 year	1233	357	28.9 (26.4-31.5)	30.6 (27.7-33.5)
2 year	901	266	29.5 (26.5-32.5)	30.7 (27.4-34.0)
3 year	1100	340	30.9 (28.2-33.6)	31.6 (28.7-34.5)
4 year	890	268	30.1 (27.1-33.1)	31.0 (27.8-34.2)
5 year	658	194	29.5 (26.0-33.0)	30.4 (26.7-34.1)
6 year	600	179	29.8 (26.2-33.5)	29.5 (25.6-33.4)
7 year	475	151	31.8 (27.6-36.0)	32.1 (27.6-36.5)
8 year	392	113	28.8 (24.3-33.3)	29.8 (25.0-34.6)
9 year	296	106	35.8 (30.3-41.3)	37.6 (31.7-43.4)
10 year	234	81	34.6 (28.5-40.1)	34.4 (28.0-40.7)
11 year	183	54	29.5 (22.8-36.2)	30.5 (23.5-37.6)
12 year	116	37	31.9 (23.3-40.5)	31.5 (22.6-40.5)
13 year	72	28	38.9 (27.3-50.4)	35.9 (24.0-47.9)
14 year	46	14	30.4 (16.6-44.2)	34.4 (18.5-50.3)
15 year	16	5	31.2 (5.7-56.8)	32.3 (2.2-62.4)

Table 4.4. Prevalence of depression up to 15 years after stroke

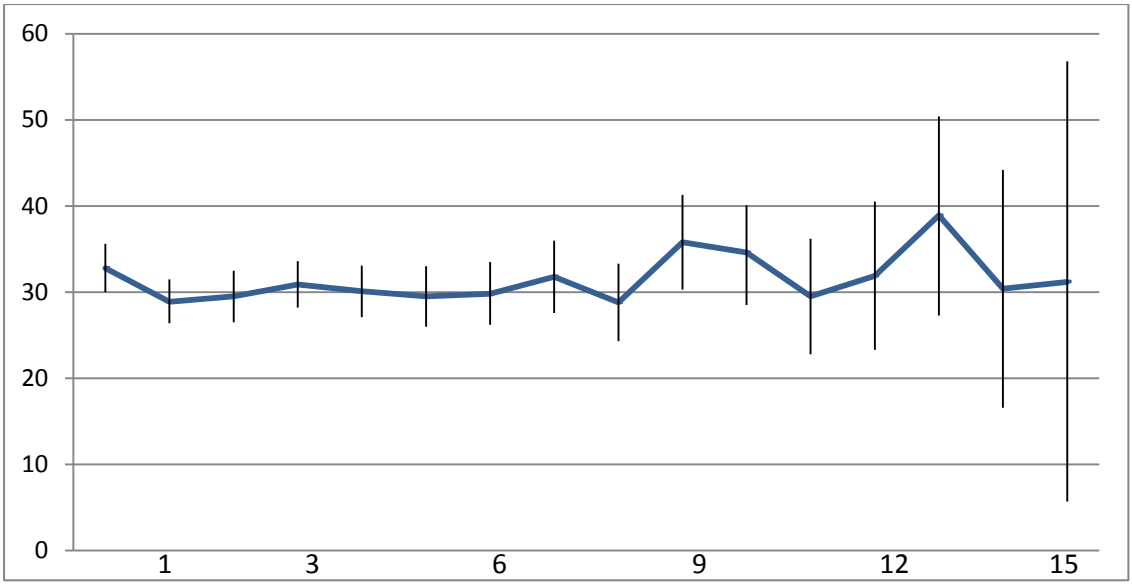


Figure 4.2 Prevalence of depression up to 15 years after stroke

4.4.2 What is the incidence of depression up to 15 years after stroke?

Crude estimates showed that between 7 and 21% of patients become depressed each year during the 15 years follow-up. Weighted estimates were very consistent with crude estimates. Crude and weighted estimates of incidence of depression up to 15 years after stroke are presented in table 4.5. Figure 4.3 shows graphic representation of crude estimates and confidence intervals.

Follow-up	Patient at risk at the beginning of each year	Patients becoming depressed	Incidence (95%CI)	Weighted Incidence (95%CI)
1 year	518	85	16.4 (13.2-19.6)	17.8 (14.0-21.6)
2 year	488	93	19.1 (15.6-22.6)	20.5 (16.6-24.5)
3 year	423	69	16.3 (12.8-19.8)	16.9 (13.0-20.8)
4 year	498	85	17.1 (13.7-20.4)	17.5 (13.7-21.2)
5 year	356	58	16.3 (12.4-20.1)	18.5 (13.8-23.1)
6 year	281	42	14.9 (10.7-19.1)	14.11 (9.5-18.7)
7 year	268	52	19.4 (14.6-24.2)	22.3 (16.1-28.6)
8 year	205	27	13.2 (8.5-17.8)	15.2 (9.4-21.1)
9 year	159	27	17.0 (11.1-22.9)	17.9 (11.0-24.9)
10 year	113	22	19.5 (12.0-26.9)	21.6 (11.9-31.2)
11 year	94	15	15.9 (8.4-23.5)	NR [h]
12 year	66	12	18.2 (8.6-27.7)	NR [h]
13 year	43	9	20.9 (8.3-33.6)	NR [h]
14 year	15	1	6.7 (0.2-26.4)[g]	NR [i]
15 year	7	1	14.3 (0.3-50.1)[g]	NR [i]

Table 4.5 Incidence of depression up to 15 years after stroke

NR: Not reported

g- Proportions calculated using “arcsine” correction

h- Weights over 25 were considered too high.

i- Estimate not reported as the arcsine correction cannot be used and weighted estimates included CIs with values over 1 or under 0.

Note: since patients who were lost to follow-up one year remained registered and were contacted again the following year, the number of patients at risk may be higher than the number of patients at risk, minus the number of incident cases, in the previous assessment

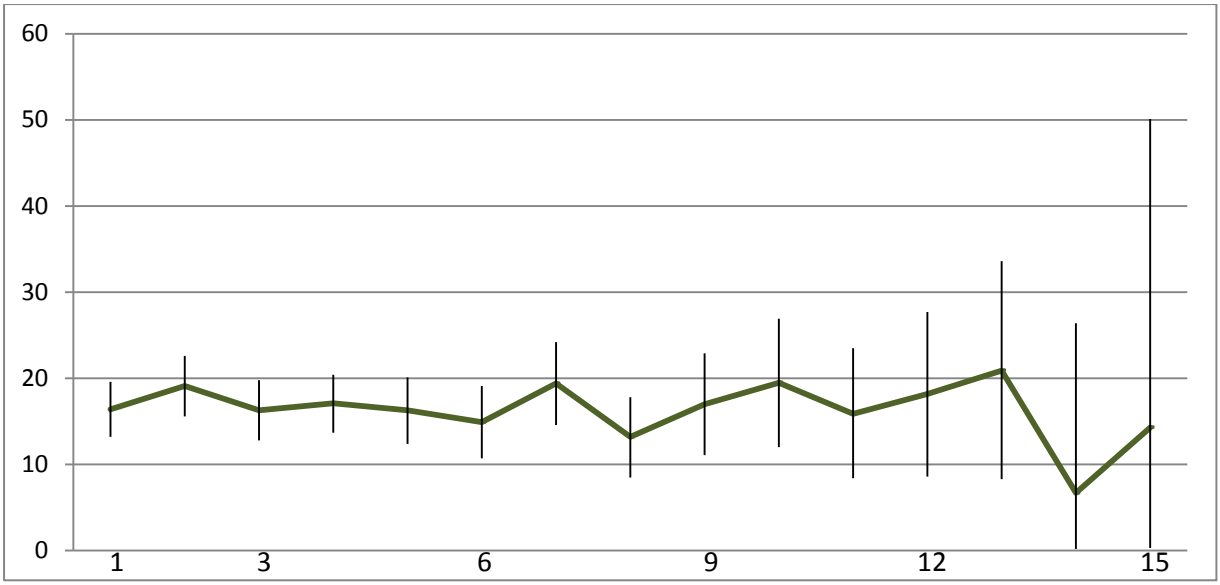


Figure 4.3 Incidence of depression up to 15 years after stroke

4.4.3 What is the cumulative incidence of depression up to 15 years after stroke?

Crude and weighted estimates of cumulative incidence show that over half of the patients have depression at some point within 15 years of stroke. (Table 4.6)

Patients assessed for depression	Patients depressed at any time point	Cumulative incidence	Weighted cumulative incidence
2183	1210	55.4 (53.3-57.5)	58.2 (52.9-60.5)

Table 4.6 Cumulative incidence of depression up to 15 years after stroke.

4.4.4 When is the onset of depression after stroke?

The proportion of patients with complete follow-up who have their first episode of depression at each time point decreases along the 15 years after stroke. At three months 33% of assessed patients had their first detected episode of depression and this proportion gradually went down to 4% in year nine. There were no observations of patients having their first episode of depression after year nine. Crude and weighted estimates were consistent throughout the follow-up. Table 4.7 presents crude and weight proportion of patients with complete follow-

up who reported their first episode of depression at each time point. Figure 4.4 shows graphic representations of crude proportions.

Follow-up	Number of patients with complete follow-up to each time point	Patients with complete follow-up and depression first detected	Proportion of patients with complete follow-up and depression first detected	Weighted proportion of patients with complete follow-up and depression first detected
3months	1101	361	32.8 (30.0-35.6)	33.2 (30.0-36.4)
1 year	750	85	11.3 (9.0-13.6)	12.0 (9.4-14.7)
2 years	450	40	8.9 (6.2-11.5)	9.4 (6.4-12.3)
3 years	329	17	5.2 (2.8-7.6)	5.6 (2.8-8.3)
4 years	249	16	6.4 (3.3-9.5)	5.2 (2.5-8.0)
5 years	154	3	1.9 (0.4-4.9)[g]	NR [i]
6 years	87	0	0	NR[h]
7 years	44	4	8.3 (0.2-16.4)[g]	NR i
8 years	36	0	0	NR [h]
9 years	27	1	3.7 (0.09-15.4)	NR [h]
10 years	14	0	0	NR [h]
11 years	11	0	0	NR [h]
12 years	5	0	0	NR [h]
13 years	No observations	-	-	-
14 years	No observations	-	-	-
15 years	No observations	-	-	-

Table 4.7 Proportion of patients with complete follow-up having first episodes of depression at each time point

NR: Not reported

g- Proportions calculated using the arcsine correction

h- Weights over 25 were considered too high.

i- Estimate not reported as the arcsine correction cannot be used and weighted estimates included CIs with values over 1 or under 0.

Note: No patients had complete follow-up from registration to more than year 12

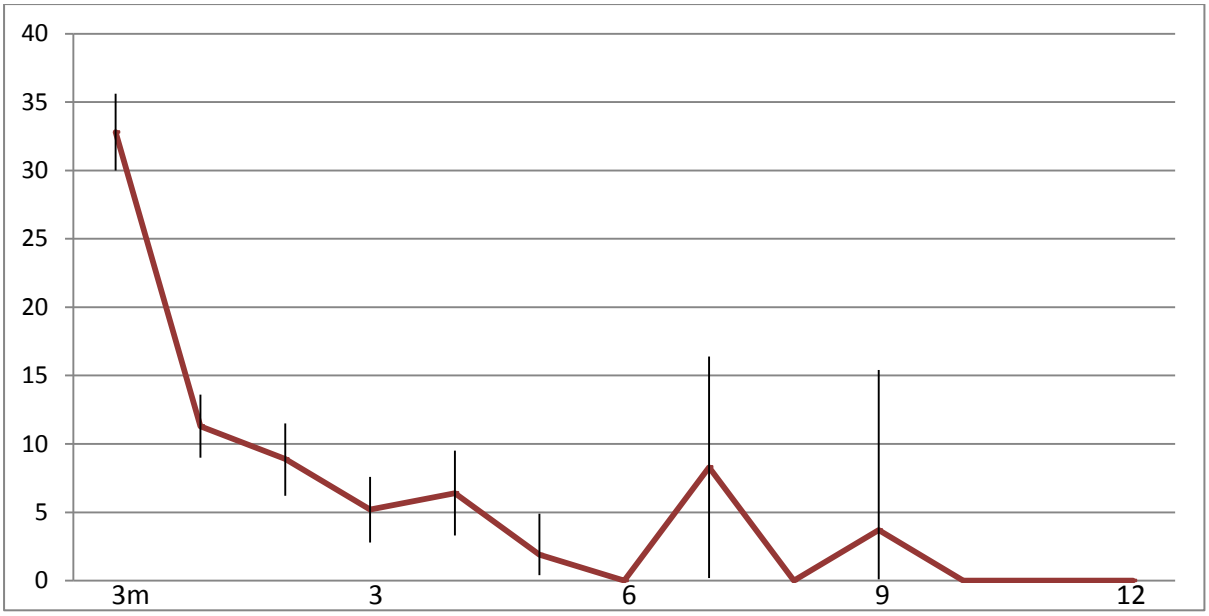


Figure 4.4 Proportion of patients with complete follow-up having first episode of depression at each time point.

4.4.5 What is the duration of the episodes of depression after stroke?

Most episodes starting at any time point had recovered the following year with a much smaller number of episodes of longer duration. The number of episodes observed decreased as the duration became longer. No episodes lasting more than nine years were observed. (Table 4.8)

As can be seen in Table 4.9 and figure 4.5, half of the patients who were depressed at three months had recovered from depression at one year. The other half recovered gradually between years two and nine. No cases of depression at three months recovering after year nine were observed. Crude and weighted estimates were consistent.

Subsequent years of depression	Episodes with complete data from onset to recovery (N=234)
1 year	175
2 years	41
3 years	9
4 years	5
5 years	1
6 years	1
7 years	1
8 years	0
9 years	1
10 years	0
11 years	0
12 years	0
13 years	0
14 years	0

Table 4.8 Duration of episodes of depression at any time point after stroke

Recovery time	Patients with depression at 3 months with complete follow-up	Patients with depression at 3months recovered for the first time	Proportion of patients depressed at 3months recovered for the first time (95%CI)	Weighted proportion of patients depressed at 3months recovered for the first time (95%CI)
1 year	232	116	50.0 (43.5-56.5)	50.3 (43.1-57.6)
2 years	139	19	13.7 (7.9-19.4)	13.9 (7.3-20.4)
3 years	92	7	7.6 (2.1-13.1)	8.1 (1.6-14.7)
4 years	74	3	4.0 (0.9-10.1)[g]	NR[j]
5 years	41	1	2.4 (0.06-10.3)[g]	NR[i]
6 years	26	1	3.8 (0.1-15.9)[g]	NR[i]
7 years	12	0	0	NR[h]
8 years	9	0	0	NR[h]
9 years	7	1	14.3 (0.3-50.1)[g]	NR[i]
10 years	5	0	0	NR[h]
11 years	5	0	0	NR[h]
12 years	2	0	0	NR[j]
13 years	0	-	-	-
14 years	0	-	-	-
15 years	0	-	-	-

Table 4.9 Patients depressed at three months recovering at each time point

NR: Not reported

g- Proportions calculated using the arcsine correction

h- Weights over 25 were considered too high.

i- Estimate not reported as the arcsine correction cannot be used and weighted estimates included CIs with values over 1 or under 0.

j- Number of observations too low to build a model of completeness.

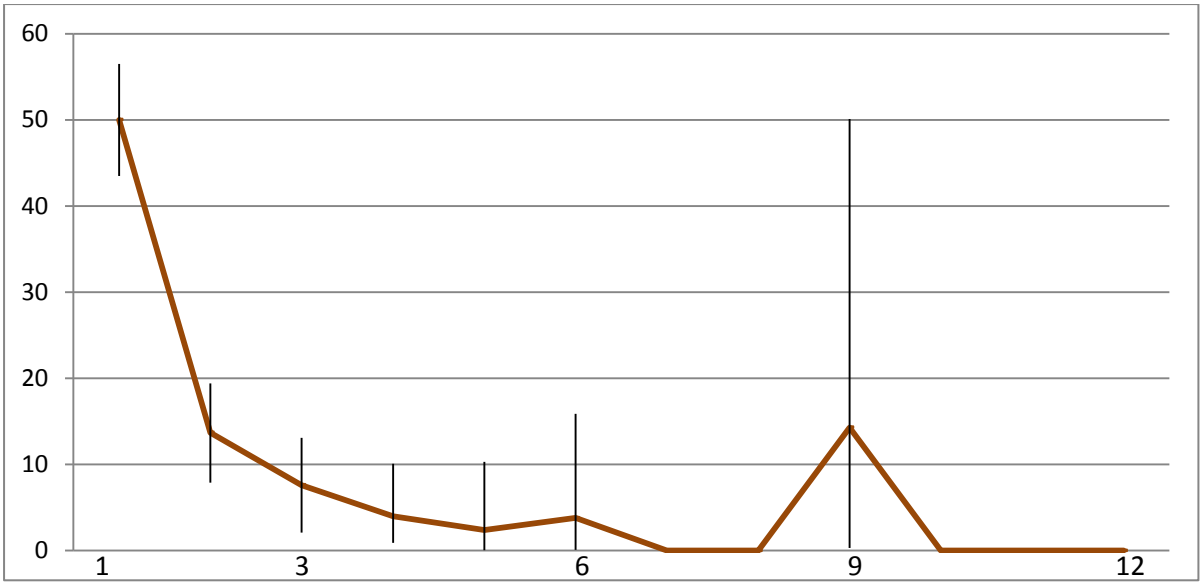


Figure 4.5 Patients depressed at three months recovering at each time point

4.4.6 What is the recurrence rate of depression after stroke?

The proportion of incident cases in which a previous episode had been observed rose from 38% in year two to 100% in years 14 and 15. (Table 4.10 and Figure 4.6)

Follow-up	N incident cases with 3 or more assessments	N of cases with at least one previous episode of depression	Proportion of recurrent cases
2 years	65	25	38.5 (26.3-50.6)
3 years	57	26	45.6(32.3-58.9)
4 years	68	29	42.6(30.6-54.7)
5 years	54	31	57.4(43.8-71.0)
6 years	40	27	67.5(52.3-82.7)
7 years	51	31	60.7(46.9-74.6)
8 years	26	20	76.9(59.6-94.3)
9 years	27	17	63.0(43.5-82.4)
10 years	22	17	77.3(58.2-96.3)
11 years	15	12	80.0(55.0-100.0)[g]
12 years	12	10	83.3(56.7-100.0)[g]
13 years	8	7	87.5(54.9-99.7)[g]
14 years	1	1	100
15 years	1	1	100

Table 4.10 Proportion of recurrent cases of depression after stroke

g- Proportions calculated using the arcsine correction

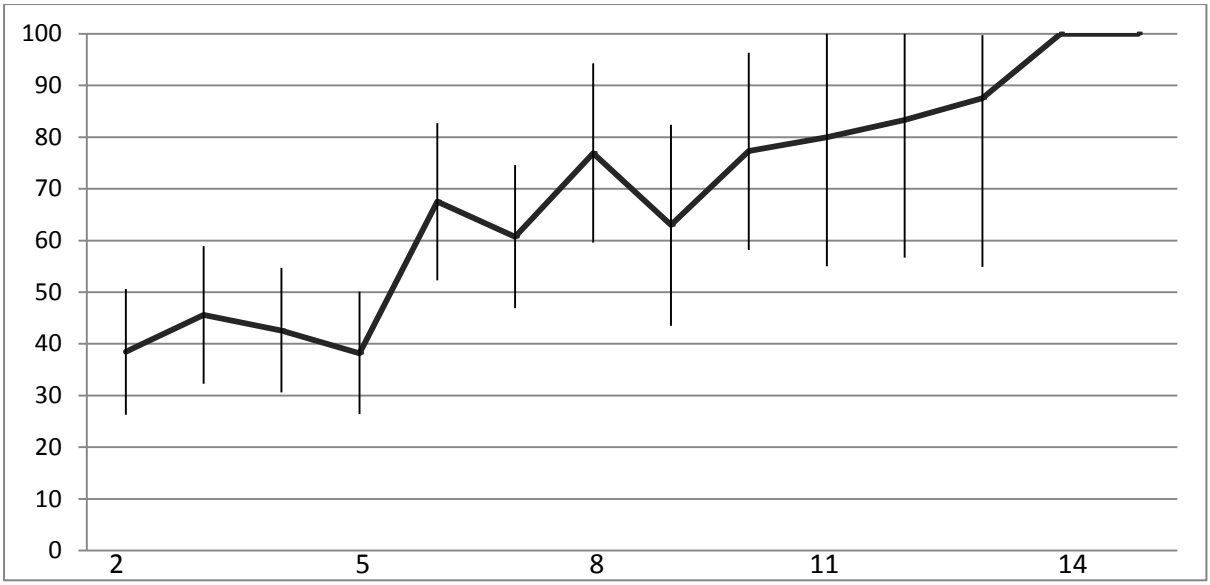


Figure 4.6 Proportion of recurrent cases of depression after stroke

The number of patients with missing recurrence data was low (28-0) It was not possible to build a stable logistic regression model to identify predictors of completeness and therefore the data was not weighted. Only crude estimates are presented. There were no incident cases from year nine with less than three assessments, therefore there was no missing data on recurrence from year nine onwards.

4.5 DISCUSSION

These observations show that depression affects half of all stroke patients at some point, with a stable prevalence of around 30% up to 15 years after stroke. However, the natural history of depression after stroke seems to be very dynamic with most patients becoming depressed shortly after stroke, recovering from depression in a few years and having a significant risk of recurrent episodes of depression in the long term.

4.5.1 Natural History

This thesis shows a prevalence of depression similar to the one previously reported in other studies with shorter follow-up conducted across the world.[60] However, in this thesis estimates

of prevalence up to 15 years after stroke are presented. The great stability of the observed prevalence should be noted as the risk of depression does not decline with time, not even in the very long term after stroke.

Incidence is an estimate of natural history that had been scarcely investigated. An incidence of 33% 13 months after stroke was reported in one study[117] and another study reported annual incidence of 10% one year after stroke.[93] The incidence of depression observed in this thesis, between 7% and 21%, almost stable throughout the follow-up, is another estimate pointing towards the persisting risk of depression amongst stroke patients and the dynamic natural history of depression in the long term after stroke.

The observed cumulative incidence shows that one in two stroke patients becomes depressed. Similar estimates had been reported before in only one study of stroke patients with two years follow-up.[236] The cumulative incidence of depression in stroke cohorts has been so rarely reported in previous studies that the overall importance of depression amongst stroke patients can be underestimated. The repeatedly reported prevalence of 30% might have lead doctors and policy makers to believe that depression affects one in three instead of one in two stroke patients as it seems to be the case.

As mentioned above, the HAD score is not stable over time therefore this thesis may have missed patients who have had depression, or have recovered from it, between the annual assessments. The management of missing data used in this thesis adds robustness to the analysis but it also has limitations, as discussed above. These limitations of may have led to an underestimation of the cumulative incidence of depression after stroke that may be over 55%. Considering the obtained result, and the fact that it may still be an underestimation, the possibility of including assessments for depression in the routine care of long term stroke survivors could be raised.

No studies were identified in the systematic review presented in Chapter two, investigating time after stroke of depression onset. The results obtained of time of onset of depression suggest that there is a moment of high risk for depression shortly after stroke. The proportion of stroke patients who have their first episode of depression more than five years after stroke is really low and there are no new cases after year nine. These observations suggest that patients not becoming depressed shortly after stroke may not become depressed at all. Although these results should be interpreted cautiously, it seems possible to identify this group of patients as low risk for depression. These results will be analysed further in the next chapter of this thesis together with other predictors of depression in the long term after stroke.

The duration of the episodes of depression is relatively short, with half of patients depressed at three months recovered at one year. Other studies of stroke patients have published similar results.[93 110 117] These observations are also consistent with the natural history of depression in general population, in which most episodes tend to have duration under one year.[16 19 237]

The increase in recurrent episodes observed during the 15 years of follow-up explains why depression starting shortly after stroke and having short duration has a stable prevalence. Patients recovering from an episode of depression remain at risk of having another one.

Studies observing general population report lower frequency of depression than the one observed in this thesis amongst stroke patients. A cohort study observing civil servants in the United Kingdom reported prevalence of depression between 12 and 14% in a 20 years follow-up, far below the observed prevalence of 30% in our SLSR cohort.[17] Several studies conducted in different countries have reported a cumulative incidence of depression between 13 and 17% during patient's life time and incidence between 5 and 10%.[15 16] However, depression after stroke seems to have similarities with depression in general population, presenting short duration and high recurrence rate.[15 16 238 239 240] As the aetiology of

depression is not entirely clear[19 31] it is difficult to explain the differences and similarities between depression after stroke and depression in general population. It has been reported that medical illness increases the risk of depression.[19 241] The World Health Survey reported a prevalence of depression between 10 and 14% in patients under general hospital care.[242] Studies on specific diseases such as Ischaemic heart disease [243 244] COPD[245] and diabetes[246] report higher prevalence of depression in patients affected by these conditions than in general population. Life threatening or chronic physical illness, unpleasant and demanding treatments and drugs that cause depression as a side effect, such as antihypertensives, corticosteroids, and chemotherapy agents may explain this association between ill health and depression.[19] Most of these apply to stroke patients. However, the increased prevalence of depression specifically amongst stroke patients is probably due to other causes as well, including the following: 1) depression is a risk factor for stroke, therefore the proportion of patients at risk of depression may be increased amongst stroke patients compared to general population; 2) depression and stroke have risk factors in common such as sedentary lifestyle, smoking and overeating; 3) depression is a secondary psychological reaction to stroke; 4) depression is secondary to other outcomes of stroke such as disability; or 5) stroke has a direct pathophysiologic effect on the brain or has indirect physiologic effects e.g.: increasing cytokine levels or other inflammatory factors that affect the brain.[247]

4.5.2 Strengths and limitations

To assess the natural history of depression it would have been ideal to follow patients up more frequently as the average duration of episodes of depression is shorter than one year.[16] With assessments at three months, one year after stroke, and then annually, it is not possible to estimate with accuracy the cumulative incidence, time of onset, duration, and the time of recovery of depression. It is possible that depression may not have been identified in some

patients. Depression may actually be affecting more than one in two stroke patients. The proportion of recurrent episodes may have been underestimated as well. Assessing the patients more frequently would have allowed obtaining more accurate estimates of cumulative incidence, time of onset, duration, and recurrence of depression after stroke. However, these are common limitations of large epidemiology studies like the SLSR. The logistic, human and financial resources used to keep the SLSR running for 15 years have been substantial. The SLSR is probably the largest cohort of stroke patients followed for so long. This provides good statistical power in all the analyses of data collected in the long term after the acute event. Another strength of this study is that data comes from a multiethnic population based register, which provides the least biased sample. This makes estimates valuable and original despite the logistic limitations.

Data on medication at follow-up, including antidepressants, is currently collected routinely in the SLSR. However, these data was incomplete in the 1995-2009 dataset used for this thesis. The natural history of depression observed in this thesis may have been modified by the treatments for depression provided by patients' doctors. However, these modifications may not be very relevant since interventions to prevent or treat depression after stroke only have a limited effect according to two Cochrane reviews.[78 79]

Like many other cohort studies the SLSR doesn't have a control arm. The only way to know if the estimates of depression observed amongst stroke patients differ from the ones of general population is by comparing them with the ones reported in other studies. One population based study of stroke patients recruited controls to allow estimates of the relative risks of depression after stroke.[91] They reported that the prevalence of depression in stroke survivors was twice that in controls, although this difference was only significant at the six months follow-up assessment. Another robust examination of the relative risk of depression

in stroke survivors was undertaken in The Framingham Study. They reported that significantly more stroke survivors were depressed than controls matched for age and gender.[189]

As in almost all cohort studies there is some missing data in this thesis. The rates of missing data are not only due to the difficulty following patients for so long but to the difficulty of some patients, particularly those with cognitive and communication impairment, to respond to the HAD questionnaire. The exclusion of patients with cognitive and communication impairment is a limitations affecting most studies of depression in stroke cohorts.[60] Missing data was handled using IPW. The assumption used to justify IPW was that data was missing at random (MAR) and the probability of being missing was modelled using baseline predictors. While IPW adjusts for differences in characteristics of patients with complete and incomplete follow-up, it cannot adjust for unmeasured factors which may result in some patients being more likely to have incomplete follow-up. If the probability of being missing had been dependent on unobserved variables, such as disability or depression at follow-up, the results obtained, despite the use of IPW, may be underestimating the relevance of depression after stroke. In that case the actual prevalence, incidence, cumulative incidence, and recurrence rate could be higher than the observed ones. It is less clear how this pattern of missing data could have affected the estimates obtained on time of onset and duration of depression. However, it is widely recognised that all methods for handling missing data are subject to bias dependent on the missing data mechanism.[248] IPW was chosen because it removed part of the bias of complete cases analysis (CC), it also has an intuitive conceptual base, easy to understand to the non mathematician, and obtaining a good model of missing patterns is easier than in multiple imputation.[231] To obtain maximum robustness both the results of CC analysis and IPW are presented. It should be noted that weighted estimates are consistent with the crude ones, with confidence intervals overlapping in all estimates. This

suggests that most of the missing data is actually missing completely at random, therefore the validity of results from CC analysis should be considered.

The method used to identify depression has strengths and weaknesses as well. The strengths and weaknesses of the HAD scale have been discussed in depth in chapter three. Despite the good performance of the HAD scale it is possible that some cases of depression may have been missed, and also that patients categorised as depressed had no depression (HAD sensitivity and specificity are 0.82 and 0.74 respectively).[217] It has been reported that Stroke survivors who score below threshold on standard depression measures may still have important negative cognitions such as hopelessness, worthlessness, or suicidality.[249]

Since the HAD scale does not have items related to somatic symptoms and neither to other mental health symptoms, such as suicidal thoughts, a number of depressed patients with these symptoms may not have been correctly categorised. The inaccuracy introduced by HAD may have affected the different estimates of natural history in both ways, leading to an under or overestimation of depression. The use of a binary variable to define depression, even when using a validated scale with good performance and a cut-off point supported by two systematic reviews,[204 205] gives no information on the severity of depression. It is possible that part of the recurrent cases may also be patients moving from scores slightly below seven to slightly above seven. It would have been ideal to assess depression with clinical diagnostic tool, such as the DSM-IV[85] or DSM-IV TR[86] instead than using a screening tool. However, the HAD scale was designed to assess depression in patients with non psychiatric medical problems, it has been widely used and numerous studies have reported its good performance. [216-219 221] In addition it would have been unfeasible to assess with DSM-IV, so many patients for such a long period of time.

4.5.3 Implications for clinical practice

These results show that depression is a very common outcome of stroke, which may affect patients many years after the acute event. According to the results obtained in this thesis disregarding depression in the long term after stroke could be wrong. Clinicians should acknowledge that depression remains a frequent active problem long after stroke even when stroke seems to be completely settled and many other medical issues may have happened. Doctors and nurses should pay special attention to patients who have recently had a stroke as this is the moment in which most patients become depressed. Except in those patients who don't become depressed shortly after stroke, that seem to be at lower risk, depression requires periodic clinical attention in the long term. To ensure this kind of attention a good coordination between primary and secondary care clinicians would be essential. As the duration of the episodes of depression is similar to the ones observed in general population, stroke patients treated for depression may need similar duration of treatment and follow-up. The high rate of recurrence of depression should also be acknowledged. Thinking that a patient recovering from depression is a "closed case" could lead to a late diagnosis or an overlooking of a further episode. An empathic communication between patient and doctor should allow discussing the good news of the recovery and the need to be alert about a possible recurrence of depression.

As a way to increase patients involvement in clinical management[250], patients and carers may need to be informed about the risk and the course of depression after stroke. It has been reported that 50 to 70% of the cases of depression general population remain undetected.[237] A possible message to be transmitted to patients and carers could include the following: If you think you are depressed, do tell your doctor because he/she may be able to help you. Please be aware that depression can happen more than once.

4.5.4 Implications for future research

The description of the natural history of depression after stroke provides valuable evidence for clinicians but raises other questions.

A Cochrane systematic review reported that antidepressants improve symptoms of depression in physically ill patients.[54] Another systematic review reported improvement of depression symptoms amongst patients with ischaemic heart disease treated for depression.[251] A number of randomised controlled trials have also reported an improvement of symptoms of depression in diabetic patients.[252-256] However, the Cochrane reviews on interventions to treat and prevent depression after stroke reported limited effect.[78 79] Considering the similarities of depression after stroke with the one observed in general population, or in other physically ill patients, it could be hypothesized that stroke patients may also have a positive response if interventions were delivered at the right time, and sustained in the long term. According to the results presented in this chapter, interventions to screen prevent and treat depression afters stroke, to be tested in future clinical trials, should start shortly after stroke and be repeated periodically. The moment of highest risk, in which interventions can be delivered, is the first year after stroke. The effect of interventions can be tested shortly after being started, as most episodes show short duration. Patients who are not depressed shortly after stroke are less likely to become depressed in the long term and therefore interventions on them are less likely to show any effect. However, patients who have depression shortly after stroke are at high risk of having a recurrent episode and studies testing interventions for these patients in the long term are needed.

It is unlikely that the risk of depression is equally distributed among stroke patients. The investigation of predictors of depression after stroke will help identifying patients at highest risk on which intervention should focus. This question will be addressed in the next chapter.

In order to treat depression after stroke, and to plan the resources required for this, the description of its natural history is no enough. A good understanding of the potential association between depression and other health outcomes is required. Chapter six will address this area.

CHAPTER 5. PREDICTORS AND ASSOCIATIONS OF DEPRESSION AFTER STROKE

5.1 ABSTRACT

Background: Evidence on the predictors of depression after stroke is insufficient to identify the patients at highest risk on which interventions should focus.

Objective: To identify sociodemographic and clinical predictors of depression up to 15 years after stroke, and to identify follow-up variables associated with depression up to 15 years after stroke.

Methods: Data from the patients with first ever strokes registered in the population-based South London Stroke Register between January 1995 and December 2009 (N at registration=4022) were used. Data were collected at time of stroke and survivors were followed up at three months, one year and annually thereafter up to 15 years after stroke. Baseline data included: age, gender, ethnicity, socioeconomic status, living conditions and stroke severity. Follow-up included assessments of social conditions (accommodation, employment, and social networks), cognition (Abbreviated Mental Test or Mini Metal State Examination), disability (Barthel Index) and activity (Frenchay Index). Follow-up also included assessments for depression (Hospital Anxiety and Depression, depression subscales scores >7 = depression). Multivariable logistic regression models adjusted for age, gender and ethnicity, were used to investigate the association of baseline and follow-up variables with depression at different time points, and also with time of onset of depression, duration, and recurrence of depression. Multiple imputation was used to handle missing data

Results: Stroke severity, disability, depression before stroke, and depression and anxiety three months after stroke, are the baseline variables most consistently associated with

depression up to 15 years after stroke. Disability, social isolation, low level of activity and cognitive impairment are the follow-up variables most consistently associated with depression at follow-up.

Conclusion: The risk of depression after stroke is significantly higher in patients with severe strokes, previous depression, and low social support. Interventions for this particular group of patients should be considered.

A summary of the results presented in this chapter was presented in the 2010 European stroke Conference and then published in Stroke in 2011. See appendix one.

5.2 INTRODUCTION

The following questions will be addressed in this chapter:

- What are the predictors of depression after stroke?

- What factors, observed at follow-up, are associated with depression after stroke?

Clinical guidelines, based on consensus, recommend that stroke patients should be screened for depression and treated whenever necessary.[76 77] The literature review presented in Chapter two showed that depression after stroke predicts other negative health outcomes at follow-up such as higher mortality. Although these results come from a small number of studies, it would be plausible that treating depression may also have a positive effect on health outcomes other than depression itself.

However, there are some issues that make the implementation of clinical guidelines difficult for the clinician when it comes to intervening on depression after stroke. Depression can be perceived by doctors, patients and carers as a natural consequence of poor health or advanced age.[257] This may lead to a quiet acceptance of the problem, underreporting of the symptoms can be an issue[60], and the clinical care provided may be inadequate.[53]

A Cochrane review concluded that selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), and noradrenergic and specific serotonergic antidepressants (NaSSA), can benefit the patients with depression and physical illness.[54] However, only eleven of the 50 studies included in this review had been conducted in stroke patients. Other studies had been conducted in patients with other diseases including Diabetes, COPD, HIV and Parkinson's disease. Two other Cochrane reviews investigating antidepressants, including SSRI, TCA and NaSSA, and psychotherapy, to treat and prevent depression in stroke patients, reported only a limited of these interventions.[78 79] The authors of these reviews raised two points to explain

the limited effect of available interventions on depression after stroke.[78 79] The first one was whether interventions had been given at the right time and for long enough to be effective. The long term natural history of depression after stroke had not been well documented previously and this imposes a difficulty on the time of delivery of the interventions. The previous chapter addressed some of the gaps in the knowledge on the natural history of depression after stroke, including its incidence, prevalence, cumulative incidence, duration and recurrence rate in the long term. This could help to decide when interventions should be delivered. The other issue raised by Cochrane reviewers is whether interventions had been given to the right patients. Depression is only one of the many possible long term outcomes of stroke but it does not affect all stroke patients. Acute stroke has an increasingly complex clinical management. Mortality during the acute phase has declined in the past decades but it is still high. Identifying patients at risk of depression in the long term may not be the stroke physician's first priority.[53] The long term follow-up of stroke survivors is mostly conducted in primary care. GPs and primary care nurses see patients who have had a stroke at some point, amongst other possible comorbidities, together with many other patients presenting different problems. It is very difficult for the primary care clinicians to screen individually for every possible long term outcome of each chronic disease of all the patients on the list. These factors make a challenge for primary and secondary care clinicians to screen for depression, and treat when needed, all stroke patients in the long term.

The association between chronic illness, not specifically stroke, and depression has been documented.[191-193] In 2009, NICE published a guideline on the treatment and management of depression in adults with chronic physical health problems.[258] Many stroke survivors can be categorised within this group. By doing this stroke patients at risk of depression are included in a proportionally larger group within the GP list. This may help them receive the care they need.

Another strategy that could be used to identify patients who may benefit from screening, prevention or treatment, of depression is to define the clinical profile of the patients at high risk of it. Focusing on high risk patients reduces the number of patients requiring attention, making interventions easier to deliver. Interventions will be more effective if they are given at the right time, and only to the patients who really need them. Furthermore, identifying predictors of depression, and its natural history, will not only help in the optimisation of available interventions but also in the development of innovative ones. Finally, treating depression effectively, and observing a positive effect on patient's mood and on other outcomes such as disability, should help clinicians to have a more proactive attitude towards stroke patients at risk of depression.

Since depression after stroke can be a chronic and recurrent problem, it would also be useful for clinicians and patients to know if any variables routinely observed at baseline can predict specific patterns of natural history e.g.: time of onset, duration or recurrence rate.

As seen in Chapter four, depression is a frequent outcome of stroke, which can affect patients both in the short and in the long term. What predicts depression, and its natural history, may also form part of the information that clinicians give to patients and carers. This information might include messages such as: "Be alert at this particular moment, about depression in case you observe these particular signs", "You may benefit from having your depression treated if we see you at the right time and we can follow you up appropriately" or "Depression in a patient with your profile is likely to last that long". A better understanding on predictors of depression should also help patients to seek medical care more appropriately and to have a better knowledge on the prognosis of the condition.

Although the main aim of this chapter is to identify predictors and associations of depression after stroke that can be used in clinical practice, it may also give valuable information on the

aetiology of depression. While the aetiology of depression is not entirely clear, it is widely accepted that there are biological, psychological and sociological factors involved.[19 31] Some of the variables investigated in this thesis will simply be statistically associated with depression. They will only be useful in clinical settings as predictors or associations of depression. Other variables statistically associated with depression will actually be aetiological factors of depression after stroke.

As presented in Chapter two, some studies have investigated potential predictors of depression after stroke. However, most of these studies have limitations including small sample size, short follow-up and weak analysis. From the available evidence, it is difficult to identify the patients at high risk of depression.[62] The contribution of these studies to the knowledge of the aetiology of depression is limited. It is also difficult to improve available interventions or to design innovative ones with the results we have. The available evidence can make very little difference to the decisions that clinicians, patients and carers take regarding depression after stroke.

This chapter tests the hypothesis that some socio-demographic and clinical variables are associated with depression after stroke making it possible to identify patients at highest risk.

The first aim of this chapter is to provide evidence on predictors of depression after stroke. Since the natural history of depression after stroke is very dynamic, this chapter will also investigate predictors of time of onset, duration, and recurrence, of depression after stroke. The second aim is to identify variables observed at follow-up that, together with the baseline predictors, may help clinicians to identify patients at high risk of depression in the long term. A good report of baseline predictors and associations of depression after stroke will help describing the clinical profile of the patients at highest risk, on which future clinical trials and available interventions should focus.

5.3 METHODS

Data from the South London Stroke Register, described in Chapter three, were used. The variables analysed in this chapter were selected for their potential clinical value to identify patients at highest risk of depression, and summarised below.

Sociodemographic and clinical variables collected at baseline were investigated as potential predictors of depression. Sociodemographic data included age, which was categorised into groups to investigate the potential effect of stroke in depression below and above the traditional age for retirement: below and above 65 years old at the time of stroke. Other sociodemographic variables investigated were gender, ethnicity (white, black and other ethnicity), employment status (working, unemployed, not working due to disability, retired, and other), socioeconomic status (manual, non manual, army), education level (no formal education, primary, secondary or tertiary) , and living conditions prior to stroke (alone, with someone, in a sheltered home, or in an institution). The distribution of sociodemographic variables investigated as predictors of depression is presented in table 5.1

Clinical variables investigated as predictors included risk factors for depression, stroke severity measures and depression and anxiety three months after stroke. Risk factors included past medical history of depression, treatment for depression at the time of stroke, smoking habit (never smoked, ex-smoker, smoker), alcohol consumption, amount of alcohol consumed per week, diabetes pre-stroke, ischaemic heart disease pre-stroke, depression three months after stroke, and anxiety three months after stroke. (Table 5.2)

		Time (years after stroke)					
		1	3	6	9	12	15
HAD completed		1233	1100	600	296	116	16
Age	0-64	481 (41.6)	469 (42.6)	296 (49.3)	181 (61.1)	70 (60.3)	9 (56.2)
	>64	752 (57.4)	631 (57.4)	304 (50.7)	115 (38.8)	46 (39.7)	7 (43.7)
Gender	Male	683 (55.4)	631 (57.4)	337 (56.2)	174 (58.8)	74 (68.8)	7 (43.7)
	Female	550 (44.6)	469 (42.6)	263 (43.8)	122 (41.2)	42 (36.2)	9 (56.2)
Ethnicity	White	865 (70.1)	765 (69.5)	412 (68.7)	199 (67.2)	82 (70.7)	10 (62.5)
	Black	276 (22.4)	254 (23.1)	144 (24.0)	75 (25.3)	26 (22.4)	4 (25.0)
	Other	76 (6.2)	66 (6.0)	39 (6.5)	19 (6.4)	8 (6.9)	1 (6.2)
	Unknown	16 (1.3)	15 (1.4)	5 (0.8)	3 (1.0)	-	1 (6.2)
Employ-ment	Working	268 (21.7)	236(21.4)	162(27.0)	89(30.1)	41(35.3)	1(20.0)
	Unemployed	35(2.8)	43(3.9)	29(4.8)	23(7.8)	7(6.0)	2(40.0)
	Unable to work	79(6.4)	76(6.9)	42(7.0)	21(7.1)	10(8.6)	1(20.0)
	Retired	780(63.3)	675(61.4)	324(54.0)	135(45.6)	51(44.0)	1(20.0)
	Student / Carer	30(2.4)	23(2.1)	15(2.5)	10(3.4)	5(4.3)	2(12.5)
	Unknown	41(3.3)	47(4.3)	28(4.7)	18(6.1)	2(1.7)	-
Socioeconomic status	Non manual	409 (33.2)	344 (31.3)	193 (32.2)	85 (28.7)	33 (28.4)	4 (25.0)
	Manual	731 (59.3)	685 (62.3)	372 (62.0)	193 (28.4)	79 (68.1)	11 (68.7)
	Army	93 (7.5)	67 (6.1)	32 (5.3)	17 (5.7)	4 (3.4)	1 (6.2)
	Unknown	-	4 (0.4)	3 (0.3)	1 (0.3)	0	0
Education level	No formal	5 (0.4)	5 (0.4)	2 (0.3)	0	0	0
	Primary	37 (3.0)	22 (2.0)	8 (1.3)	1 (0.3)	0	0
	Secondary	386 (31.3)	219 (19.9)	24 (4.0)	5 (1.7)	1 (0.9)	0
	Tertiary	39 (3.2)	24 (2.2)	6 (1.0)	0	0	0
	Unknown	766 (62.1)	830 (75.4)	560 (93.3)	290 (98.0)	115 (99.1)	16 (100)
Living conditions pre-stroke	Home alone	369 (29.9)	334 (30.4)	157 (26.2)	74 (25.0)	31 (26.7)	5 (31.2)
	Home with others	644 (52.3)	556 (50.5)	301 (50.2)	144 (48.6)	76 (65.5)	10 (62.5)
	Sheltered home	57 (4.6)	30 (2.7)	8 (1.3)	1 (0.3)	1 (0.9)	1 (6.2)
	Institution	13 (1.0)	5 (0.4)	3 (0.5)	0	1 (0.9)	0
	Unknown	150 (12.2)	175 (15.9)	131 (21.8)	77 (26.0)	7 (6.0)	0

Table 5.1 Sociodemographic variables investigated as predictors of depression after stroke n (%)

		Time (years after stroke)					
		1 y	3y	6y	9y	12y	15y
Depression pre-stroke	No	589 (47.8)	502(45.6)	189 (31.5)	134 (45.3)	88 (75.9)	12 (75.0)
	Yes	79 (6.4)	61 (5.5)	36 (6.0)	26 (8.8)	19 (16.4)	3 (18.7)
	Unknown	564 (45.8)	537 (48.8)	375 (62.5)	136 (45.9)	9 (7.8)	1 (6.25)
Treatment for depression pre-stroke	No	1006(81.6)	890 (80.9)	461 (76.8)	220 (74.3)	105 (90.5)	15 (93.7)
	Yes	70 (5.7)	52 (4.7)	25 (4.2)	8 (2.7)	5 (4.3)	1 (6.2)
	Unknown	157 (12.7)	158 (14.4)	114 (19.0)	68 (23.0)	6 (5.2)	0
Smoking	Never	421(32.4)	357(32.4)	207(34.5)	97(32.8)	37(1.9)	6(37.5)
	Ex-smoker	353(28.7)	319(29.0)	146(24.3)	64(21.6)	29(25.0)	7(43.7)
	Smoker	432(35.1)	396(36.0)	238(39.7)	132(44.6)	50(43.1)	2(12.5)
	Unknown	25(2.0)	28(2.5)	9(1.5)	3(1.0)	0	1(6.2)
Drinks Alcohol	No	408(33.1)	330(30.0)	174(29.0)	77(26.0)	21(18.1)	3(18.7)
	Yes	731(59.3)	673(61.2)	370(61.7)	195(65.9)	91(78.4)	12(75.0)
	Unknown	93(7.5)	97(8.8)	56(9.3)	24(8.1)	4(3.4)	1(6.2)
Alcohol intake (Units/week)	0	407(33.0)	329(29.9)	174(29.0)	77(26.0)	21(18.1)	3(18.7)
	1-14	412(33.4)	383(34.8)	200(33.3)	99(33.4)	52(44.8)	11(68.7)
	14-21	57(4.6)	46(4.2)	22(3.7)	10(3.4)	2(1.7)	-
	>21	155(12.6)	157(14.3)	94(15.7)	56(18.9)	30(25.9)	1(6.2)
	Unknown	202(16.4)	185(16.8)	110(18.3)	54(18.2)	11(9.5)	1(6.2)
Diabetes pre-stroke	No	962(78.0)	856(77.8)	456(76.0)	233(78.7)	97(83.6)	14(87.5)
	Yes	224(18.2)	194(17.6)	102(17.0)	43(14.5)	15(12.9)	2(40.0)
	Unknown	47(3.8)	50(4.5)	42(7.0)	20(6.8)	4(3.4)	0
Ischaemic heart Disease pre-stroke	No	865 (70.1)	863 (78.4)	469 (78.2)	242 (81.8)	97 (83.6)	13 (81.2)
	Yes	185 (15.0)	193 (17.5)	94 (15.7)	34 (11.5)	15 (12.9)	3 (18.7)
	Unknown	183 (14.8)	44 (4.0)	37 (6.2)	20 (6.8)	4 (3.4)	0

Table 5.2 Risk factors investigated as potential predictors of depression after stroke n (%)

Stroke severity measures investigated as potential predictors, collected during the acute phase of stroke included the following: Glasgow Coma Score (GCS) at the time of maximum impairment, which was categorised as 3-8 severe, 9-12 moderate, and 13-15 mild impairment of consciousness, dysphagia, urinary incontinence, visual field defects, neglect, dysphasia, dysarthria, paresis, cerebellar symptoms and stroke subtype (ischaemic or haemorrhagic). Cognitive function was also assessed at baseline with the Mini Mental State examination (MMSE)[209 259] except from the period between 2001 and 2006 when the Abbreviated Memory Test (AMT)[210] was used. Patients with MMSE score <24 or AMT Scores 0-7 were considered cognitively impaired.[209 210] Finally, disability was assessed seven days after stroke, using the Barthel Index (BI)[211 260]: scores of 0-14 were categorised as severe

disability, 15-19 moderate disability, and 20 independent. The distribution of clinical variables investigated as predictors of depression is presented in tables 5.3 and 5.4

Follow-up was by postal questionnaire or interview at three months, one year after stroke and annually thereafter. At follow-up patients were assessed for depression and anxiety, using the Hospital Anxiety and Depression scale (HAD).[214] Patients with a score > 7 in the depression or anxiety subscales were considered to have depression or anxiety respectively.[218] HAD was routinely collected between 1997 and 2006. Patients registered in 1995 (n=299) were not assessed at three months and one year but were in subsequent follow-ups. Patients registered in 1996 (n=350) were not assessed at three months but were at subsequent follow-ups. Data on HAD was therefore not included from these patients in the respective estimates for early rates of depression. As HAD cannot be answered by proxy, no data could be collected from patients unable to respond to the questionnaire. These included patients who had a cognitive deficit, severe disability, communication difficulties or multiple comorbidities that the fieldworker, or the patient's next of kin in case of a postal questionnaire, judged such that the completion of the questionnaire would be invalid.

		Time (years after stroke)					
		1 y	3y	6y	9y	12y	15y
GCS at maximum impairment	3-8	40 (3.2)	40(3.6)	21(3.5)	15(5.1)	7(6.0)	1(6.25)
	9-12	71 (5.8)	81(7.4)	34(5.7)	16(5.4)	10(8.6)	0
	13-15	1089(88.3)	946(86.0)	528(88.0)	261(88.2)	97(83.6)	15(93.7)
	Unknown	33 (2.7)	33(3.0)	17(2.8)	4(1.3)	2(1.7)	0
Swallowing test results	Pass	873 (71.0)	787(71.6)	444(74.0)	225(76.0)	82(70.7)	14(87.5)
	Fail	241(19.6)	222(20.2)	114(19.0)	55(18.6)	29(25.0)	2(12.5)
	Unknown	115(9.4)	90(8.2)	42(7.0)	16(5.4)	5(4.3)	0
Urinary Incontinence	No	896(72.7)	801(72.8)	469(78.2)	240(81.1)	84(72.4)	13(81.2)
	Yes	298(24.2)	263(23.4)	104(17.3)	49(16.5)	29(25.0)	3(18.7)
	Unknown	39(3.2)	36(3.3)	27(4.5)	7(2.4)	3(2.6)	0
Visual field defect	No	793(64.3)	828(75.3)	467(77.8)	236(79.7)	87(75.0)	15(93.7)
	Yes	195(15.8)	201(18.3)	100(16.7)	43(14.5)	15(12.9)	1(6.2)
	Unknown	245(19.9)	71(6.4)	33(5.5)	17(5.7)	14(12.1)	0
Neglect	No	826(67.0)	851(77.4)	481(80.2)	234(79.0)	88(75.9)	16(100)
	Yes	222(18.0)	193(17.5)	86(14.3)	39(13.2)	14(12.1)	0
	Unknown	185(15.0)	56(5.1)	33(5.5)	23(7.8)	14(12.1)	0
Dyphasya	No	834(67.6)	823(74.8)	449(74.8)	219(73.9)	84(72.4)	15(93.7)
	Yes	230(18.6)	249(22.6)	134(22.3)	72(24.3)	28(24.1)	1(6.25)
	Unknown	28(2.5)	28(2.5)	17(2.8)	5(1.7)	4(3.4)	0
Dysarthria	No	525(42.6)	519(47.2)	269(44.8)	133(44.9)	53(45.7)	9(56.2)
	Yes	417(33.8)	392(35.6)	200(33.3)	84(28.4)	46(39.7)	7(43.7)
	Unknown	291(23.6)	189(17.2)	131(21.8)	79(26.7)	17(14.7)	0
Paresis	No	326(26.4)	315(28.6)	191(31.8)	99(33.4)	32(27.6)	3(18.7)
	Yes	752(70.0)	773(70.3)	402(67.0)	196(66.2)	83(71.5)	13(81.2)
	Unknown	155(12.6)	12(1.1)	7(1.2)	1(0.3)	1(0.9)	0
Cerebellar symptoms	No	966(78.3)	878(79.8)	494(82.3)	253(85.5)	100(86.2)	15(93.7)
	Yes	224(18.2)	178(16.2)	84(14.0)	31(10.5)	7(6.0)	1(6.2)
	Unknown	43(3.5)	44(4.0)	22(3.7)	12(4.0)	9(7.8)	0
Subtype	Infarct	1032(83.7)	887(80.6)	473(78.8)	225(76.0)	85(73.2)	11(68.7)
	Haemorr.	171(13.9)	175(15.9)	108(18.0)	61(20.6)	25(21.5)	4(25.0)
	Unknown	30(2.4)	38(3.4)	19(3.2)	10(3.2)	6(5.2)	1(6.2)
Cognitive level	Impaired	230(18.6)	200(18.2)	83(13.8)	39(13.2)	24(20.7)	2(12.5)
	Intact	639(51.8)	511(46.4)	260(43.3)	127(42.9)	51(44.0)	13(81.2)
	Unknown	364(29.5)	389(35.4)	257(42.8)	130(43.9)	41(35.3)	1(6.2)
Disability (Barthel index 7 days post-stroke)	Severe disability	442(35.8)	381(34.6)	181(30.2)	85(28.7)	47(40.5)	5(31.2)
	Mild disability	222(18.0)	207(18.8)	100(16.7)	48(16.2)	21(18.1)	4(25.0)
	Indepen-dence	403(32.7)	345(31.4)	224(37.3)	115(38.8)	42(36.2)	6(37.5)
	Unknown	166(13.5)	167(15.2)	95(15.8)	48(16.2)	6(5.2)	1(6.2)

Table 5.3 Stroke severity measures investigated as predictors of depression after stroke. n (%)

		Time (years after stroke)					
		1 y	3y	6y	9y	12y	15y
Depression 3 months after stroke	No	518 (42.0)	369 (33.5)	177 (29.5)	63(21.3)	16(13.8)	0
	Yes	232 (18.8)	152(13.8)	71(11.8)	25(8.4)	11(9.5)	0
	Unknown	483 (39.2)	579(52.6)	352(58.7)	208(70.3)	89(76.7)	16(100)
Anxiety 3 months after stroke	No	512(41.5)	361(32.8)	160(26.7)	55(18.6)	14(12.1)	0
	Yes	243(19.7)	163(14.8)	92(15.3)	33(11.1)	13(11.2)	0
	Unknown	478(38.8)	576(52.4)	348(58.0)	208(70.3)	89(76.7)	16 (100)

Table 5.4 Depression and anxiety in the three months after stroke n (%)

Data collected at follow-up, investigated as potential associations of depression after stroke is presented in tables 5.5 and 5.6. It included living circumstances (alone, with other, or in an institution), employment (working, unemployed, unable to work due to disability, retired and other), smoking habit (smoker or non smoker), alcohol intake, amount of alcohol consumed per week, cognitive impairment, disability, and activity level. Activity level was assessed with the Frenchay Activity Index (FAI) (inactive 0-15, moderate inactivity 16-30, or active 31-45).[223] Finally social networks were examined with two questions: Do you see as much of your relatives as you would like? (Yes/No/Don't have any). Do you see as much of your friends as you would like? (Yes/No/Don't have any).

Time (years after stroke)		1y	3y	6y	9y	12y	15y
Living circumstances	Private house alone	375(30.4)	334(30.4)	176(29.4)	100(33.8)	34(29.3)	3(18.7)
	P. house with other	669(54.3)	575(52.3)	336(56.7)	153(51.7)	53(45.7)	6(37.5)
	Institution	174(14.1)	168(15.3)	75(12.5)	37(12.5)	23(19.8)	6(37.5)
	Other	9(0.7)	8(0.7)	3(0.5)	3(1.0)	0	0
	Unknown	5(0.4)	15(1.4)	5(0.8)	3(1.0)	6(5.2)	1(6.25)
Employment	Working	89(8.6)	114(10.4)	77(11.7)	25(8.5)	9(8.0)	2(12.5)
	Unemployed	17(1.6)	132(12.0)	109(18.2)	73(24.8)	58(51.3)	12(75.0)
	Unable	163(15.7)	154(14.0)	74(12.4)	41(13.9)	8(7.1)	0
	Retired	587(56.7)	575(52.5)	338(56.5)	152(51.7)	35(31.0)	0
	Carer	7(0.7)	3(0.3)	0	0	0	0
	Unknown	172(16.6)	118(10.7)	7(1.2)	3(1.02)	3(2.6)	2(12.5)
Have someone to turn to	Yes	1024(83.0)	949(86.3)	561(93.5)	277(93.6)	106(91.4)	14(87.5)
	No	49(4.0)	44(4.0)	32(5.3)	14(4.7)	6(5.2)	2(12.5)
	Unknown	160(13.0)	107(9.7)	7(1.2)	5(1.7)	4(3.4)	0
Sees relatives enough	Yes	749(60.7)	687(62.4)	426(71.0)	212(71.6)	88(75.9)	14(87.5)
	No	293(23.8)	287(26.1)	158(26.3)	74(25.0)	24(20.7)	2(12.5)
	Don't have any	30(2.4)	19(1.7)	13(2.2)	5(1.7)	2(1.7)	0
	Unknown	161(13.0)	107(9.7)	3(0.5)	5(1.7)	2(1.7)	0
Sees friends enough	Yes	739(59.9)	671(61.0)	409(68.2)	202(68.2)	89(76.7)	14(87.5)
	No	272(22.1)	260(23.6)	150(25.0)	78(26.3)	24(20.7)	2(12.5)
	Don't have any	58(4.7)	61(5.5)	36(6.0)	11(3.7)	1(0.9)	0
	Unknown	164(13.3)	108(9.8)	5(0.8)	5(1.7)	2(1.7)	0

Table 5.5 Sociological variables collected at follow-up investigated as associations of depression n (%)

Time (years after stroke)		1y	3y	6y	9y	12y	15y
Smoking status	No	867(70.5)	809(73.5)	461(77.3)	227(76.9)	92(80.0)	13(81.2)
	Yes	353(28.7)	289(26.3)	133(22.3)	67(22.7)	23(20.0)	3(18.7)
	Unknown	9(0.7)	2(0.2)	2(0.3)	1(0.3)	0	0
Drink alcohol	No	613(49.8)	559(50.9)	292(48.8)	135(45.6)	62(53.9)	10(62.5)
	Yes	615(49.9)	536(48.8)	305(51.0)	159(53.7)	53(46.1)	6(37.5)
	Unknown	4(0.3)	3(0.3)	1(0.2)	2(0.7)	0	0
Alcohol intake (units/week	None	611(49.5)	556(50.8)	290(48.4)	139(46.9)	64(55.2)	10(62.5)
	<1	115(9.3)	0	69(11.5)	39(13.2)	8(6.9)	0
	<14	330(26.8)	395(35.9)	142(23.7)	68(23.0)	27(23.3)	2(12.5)
	14-21	55(4.5)	53(4.8)	36(6.0)	10(3.4)	3(2.6)	0
	>21	76(6.2)	54(5.9)	25(4.2)	20(6.8)	2(1.7)	2(12.5)
	Unknown amount	22(1.8)	6(0.5)	17(2.8)	6(2.0)	6(5.2)	1(6.2)
	Unknown if drinks	24(1.9)	33(3.0)	20(3.3)	14(4.7)	6(5.2)	1(6.2)
Anxiety	No	818(64.3)	739(67.2)	395(65.8)	195(65.9)	69(59.5)	9(56.3)
	Yes	394(31.9)	343(31.2)	197(32.8)	97(32.8)	46(39.7)	7(43.7)
	Unknown	21(1.7)	18(1.6)	8(1.3)	4(1.3)	1(0.9)	0
Cognitive impairment	Impaired	216(19.9)	198(18.0)	99(16.5)	45(15.2)	15(12.9)	3(18.7)
	Intact	743(68.6)	618(56.2)	389(64.8)	191(64.5)	42(36.2)	5(31.2)
	Unknown	124(11.4)	284(25.8)	112(18.7)	60(20.3)	59(50.9)	8(50.0)
Disability (Barthel index)	Severe disability	211(17.1)	190(17.3)	97(16.2)	57(19.3)	36(31.0)	4(25.0)
	Mild disability	442(35.8)	396(36.0)	241(40.2)	108(36.5)	30(25.9)	6(37.5)
	Independence	562(45.7)	472(42.9)	257(42.8)	122(41.2)	41(35.3)	0
	Unknown	16(1.3)	42(3.8)	5(0.8)	9(3.0)	9(7.8)	1(20.0)
Frenchay activity level	Inactive	490(39.7)	450(40.9)	231(38.5)	116(39.2)	52(44.8)	9(56.2)
	Moderately active	420(34.0)	386(35.1)	216(36.0)	106(35.8)	32(27.6)	3(18.7)
	Active	249(20.2)	203(18.4)	114(19.0)	53(17.9)	14(12.1)	1(6.2)
	Unknown	74(6.0)	61(5.5)	39(6.5)	21(7.1)	18(15.5)	3(18.7)

Table 5.6 Clinical variables collected at follow-up investigated as associations of depression n (%)

5.3.1 Statistical Methods

Predictors, or associations, of depression assessed every three years during the 15 years of follow-up were investigated, that is predictors or associations of depression identified at one, three, six, nine, twelve and fifteen years after stroke. There were several reasons why the analyses were limited to depression observed in three years intervals: The study of the natural history of depression after stroke presented in Chapter four showed that most episodes of depression last less than one year, therefore observing patients in three years intervals should

be long enough yet not too long to give a clear image of incident and recurrent cases. Making six observations during a period of 15 years gives a consistent picture of the variables predictive of, or associated with depression in the long term. These analyses avoid examining associations at all time points as that would results in a great number of statistical associations by chance.

Potential predictors or associations of depression were first investigated with unadjusted logistic regression models. Variable showing association with depression at any time point ($p<0.1$), were then investigated with multivariate logistic regression, adjusting all models for age, gender and ethnicity. The multivariate statistical models were built following guidelines for prospective studies in stroke cohorts: The analysis was conducted using logistic regression as it is the recommended statistical approach when the outcome is the presence of depression.[74] Other approaches, such as linear regression, have been recommended for the analysis of severity of depression. Age, gender and ethnicity were considered potential confounders and therefore were included in the models.[74] There is no statistical test to identify a confounder so the variables introduced in a model remain a matter of judgement. It was decided not to force other variables into the model as the independence of variables representing clinical severity could not be demonstrated. The interpretation of the results would have been more difficult as well. The models used intended to give a clear indication of the possible association between the variable investigated and depression after stroke. The models served a double purpose. In the first part of the analysis, the focused was on predictive models (aiming to calculate the probability that an event occurring) and only included readily available pre- and acute stroke variables. In the second part of the analysis, the models intended to explain the relationship between each independent variable and depression. They were therefore explanatory and also included variables collected at the same time as depression was assessed.[74] The sample size was adequate to build the model. The

guideline is ten outcome events per independent variable entered into a logistic regression model.[74] The number of cases with the outcome of interest (depression) and the total number of cases in the sample were reported. All independent variables (or risk factors) have been clearly described, including when the variable was measured, how it was measured and coded, and in what form it was entered into the model. There was also an adequate number of people with each risk factor for the model. Important confounders, such as age, gender and ethnicity, were included into the model. Automated methods, which can select data only for being statistically significant rather that clinically meaningful, were not used.[74 185] Reporting the usefulness of the model included 95% confidence intervals around odds ratios. As age could modify the association between some of the variables analysed and depression, interactions between age and all predictors showing significant association with depression were examined. The interactions between age and employment, Barthel score, Frenchay score and cognitive impairment at follow-up, were also analysed.[26 88]

In a second stage the natural history of depression was investigated by examining the predictors of the following outcomes: depression identified at any time point of the follow-up; time of onset of depression, this is the point after stroke in which patients were first observed to be depressed; duration of depression; recurrence of depression. Predictors were first investigated in univariate logistic regression models. Those variables showing association with the outcome ($p<0.1$) were then investigated adjusting for age, gender and ethnicity following the statistical methods described above.

To analyse the predictors of time after stroke of depression onset a binary variable was defined: 0 (depression starting after three months), 1 (depression starting at three months).

Another binary variable was defined to analyse the predictors of duration of depression starting at three month: 0 (short duration: depression at three months recovered at one year), 1

(long duration: depression at three months recovering after one year). These analyses focused on depression at three months and one year as three months after stroke is the point of highest risk for depression and half of the patients depressed at this point have recovered one year after stroke (Chapter four).

To analyse predictors of recurrent depression a binary variable was defined 0 (patients with incident depression at any time point, alive in year two, who had got at least one depression assessment before and were not depressed) and 1 (patients with incident depression at any time point, alive in year two, who have been found to be depressed in at least one assessment before).

In order to define the profile at baseline of patients at highest risk of depression at any time point, predictors of depression identified in the analysis, e.g.: inability to work and paresis, were combined into a single binary variable 0/1 were 1 represented unable to work with paresis. These variables allowed to quantify the risk of having depression for patients fitting a specific profile and ultimately to define the profile of patients at highest risk. In a similar way the profile of patients at lowest risk of depression was investigated. Low risk was defined as risk of depression below 15% during the 15 years of follow-up as several studies conducted in different countries have reported a cumulative incidence of depression in general population between 13 and 17% during patient's life time.[15 16] Several variables combining predictors of high or low risk were created. The number of individual variables included was kept to the minimum to identify a clinical profile as wide as possible, of patients with high or low risk of depression.

5.3.1.1 Missing data management:

Only patients with the outcome variable observed were included, this is patients who had been assessed for depression. Most variables analysed as potential predictors had some

missing data. A separate category was assigned to it e.g.: Dysphasia 0 (No), 1 (Yes), and 2 (Missing). Sensitivity analysis was conducted to compare estimates obtained when the category for missing data was included and when it was not included. Estimates and standard errors obtained when using a missing data category were stable and similar to those based on complete data. Therefore, in order to use the maximum available data, for these variables, we reported the results using the categories for missing data.

However, as detailed in previous chapter, this approach can still introduce bias when patients with missing data are different from those with complete data. There are three patterns of distribution for missing data.[261] One of them assumes that data is missing completely at random (MCAR), which is the possibility of being missing is not associated with any observed or unobserved variables. The second one assumes that distribution of missing data depends on observed variables, which is missing at random (MAR). The last pattern assumes that missing data depends on not observed variables, which are missing not at random (MNAR). It was not possible to assume that data was MCAR, as there were associations between some of the observed variables and the possibility of being missing e.g.: Patients with higher levels of disability or cognitive impairment were less likely to respond to the follow-up questionnaire than those not disable and without impaired cognition. Therefore the MAR assumption was more plausible. The possibility of data being missing depending on not observed variables (MNAR) was also considered. However, some of the observed variables were actually associated with the possibility of being missing. Furthermore, the methods needed to conduct statistical analysis under the MNAR assumption are still being developed and are not routinely used. Hence the MAR assumption was chosen as it was plausible and the knowledge and software to work with it was available. How could the results be biased if the MNAR assumption was true is also discussed at the end of this chapter.

Estimates of the effect of variables with more than 15% of missing data missing can be specially biased. Therefore, in order to remove bias coming from missing data, under the MAR assumption, a second multivariate analysis was conducted using multiple imputation (MI).[233] MI was considered the most appropriate method as simpler methods can only deal with missing outcomes but not with missing covariates. Other methods for missing covariates are much more complex. The sophisticated statistical software needed to conduct MI analysis is available.[234] MI aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them.[233 262] The first stage is to create multiple copies of the dataset, with the missing values replaced by imputed values. These are sampled from their predictive distribution based on the observed data. The imputation procedure accounts for all uncertainty in predicting the missing values by injecting appropriate variability into the multiple imputed values; we can never know the true values of the missing data. MI is very flexible as it covers many data structures. The second stage is to use standard statistical methods to fit the model of interest to each of the imputed datasets. Estimated associations in each of the imputed datasets will differ because of the variation introduced in the imputation of the missing values, and they are only useful when averaged together to give overall estimated associations. Valid inferences are obtained because we are averaging over the distribution of the missing data given the observed data.

For variables with missing data under 15% the sensitivity analysis was considered enough to obtain robust reliable estimates and therefore MI was not used. For variables with missing data over 25% the impact of imputation error was considered too large. MI was used for variables with 15 to 25 % missing data.[234 263] Variables in the imputation models included the outcome variable (depression), all the variables included as confounders in the analysis of predictors, that is age, gender and ethnicity, the predictor being investigated, and finally

variables considered to be associated with the possibility of being missing: GCS, paresis, incontinence and Barthel index at baseline. The number of imputations equalled the percentage of patients with at least one missing variable.[234] MI was conducted, as well as the rest of the statistical analysis of this thesis with Stata 11

5.4 RESULTS:

Between 1995 and 2009, 4022 patients were registered in the SLSR. The number of patients registered in each period, assessed for depression or lost to follow-up, at each time point, has been presented in figure 4.1.

5.4.1 Predictors of depression 1, 3, 6, 9, 12, and 15 years after stroke:

All the baseline variables except the amount of alcohol consumed per week, dysarthria, cerebellar symptoms and stroke subtype, were associated with depression in the univariate analysis ($p>0.1$) at least at one time point post stroke. In the adjusted analysis being unable to work at baseline was the sociodemographic variable more frequently associated with depression, showing a significant association in years 1, 3 and 6. Female gender predicted depression in years one and three. Age under 65 predicted depression in year three and manual socioeconomic status predicted depression in year nine. The ORs and 95% CIs of the associations between all investigated sociodemographic variables and depression at 1, 3, 6, 9, 12 and 15 years after stroke adjusted by age, sex and ethnicity are presented in table 5.7.

In the adjusted analysis, depression three months after stroke and anxiety three months after stroke, together with dysphagia, paresis, impaired cognition, being a smoker, and severe disability in the acute phase were all associated with depression in at least three time points. Ischaemic heart disease pre stroke, low GCS score, urinary incontinence, visual defect and neglect in the acute phase were also identified as clinical predictors of depression. The ORs

and 95% CIs and p values of the association between clinical variables and depression up to 15 years after stroke are presented in table 5.8, 5.9 and 5.10. No significant interactions were identified in the analysis of predictors.

The association between some of the variables and depression more than six years after stroke could not be tested as the number of patients was too low to fit a stable regression model.

		Time (years after stroke)					
		1	3	6	9	12	15
Age	0-64	1	1	1	1	1	1
	>64	0.79 (0.61-1.03)	0.67 (0.52-0.87)**	0.99 (0.69-1.41)	0.88 (0.53-1.44)	1.25 (0.56-2.79)	0.19 (0.01-3.05)
Gender	Male	1	1	1	1	1	1
	Female	1.29 (1.00-1.66)*	1.41 (1.08-1.83)**	0.91 (0.64-1.31)	1.54 (0.94-2.53)	0.92 (0.40-2.11)	0.47 (0.03-6.24)
Ethnicity	White	1	1	1	1	1	1
	Black	0.78 (0.57-1.07)	0.94 (0.69-1.29)	1.0 (0.65-1.52)	0.76 (0.42-1.37)	0.81 (0.30-2.18)	0.41 (0.02-7.41)
	Other	2.02 (1.25-3.27)**	1.44 (0.85-2.43)	2.12 (1.08-4.12)*	2.01 (0.77-5.22)	2.18 (0.50-9.46)	-
Employ-ment	Working	1	1	1	1	1	1
	Unemployed	1.76 (0.83-3.75)	1.95 (1.00-3.82)	1.42 (0.60-3.37)	3.18(1.20-8.42)**	2.15 (0.38-12.11)	-
	Unable to work	2.70 (1.59-4.61)**	1.66 (0.97-2.86)	2.41 (1.18-4.94)*	4.38 (1.60-12.00)**	0.13(0.01-1.48)	-
	Retired	1.46 (0.95-2.25)	1.48 (0.96-2.28)	1.18(0.68-2.04)	0.87 (0.40-1.90)	0.37 (0.09-1.56)	-
	Other	1.90 (0.85-4.23)	1.18 (0.47-2.95)	1.61(0.49-2.95)	3.09 (0.78-12.26)	9.28 (0.88-98.09)	-
Social class	Non manual	1	1	1	1	1	1
	Manual	1.11 (0.85-1.47)	1.33 (0.99-1.77)	1.01 (0.68-1.49)	2.16 (1.20-3.89)**	1.49 (0.57-3.89)	-
Education level	No formal	1	1	1	1	1	1
	Primary	0.18 (0.02-1.85)	1.47 (0.20-10.84)	-	-	-	-
	Secondary	0.11 (0.01-0.98)	0.55 (0.09-3.42)	-	-	-	-
	Tertiary	0.05 (0.004-0.53)	0.32 (0.04-2.61)	-	-	-	-
Living conditions pre-stroke	Home alone	1	1	1	1	1	1
	Home with others	0.82 (0.62-1.10)	0.80 (0.60-1.08)	1.08 (0.69-1.71)	1.25 (0.67-2.32)	0.66 (0.26-1.64)	-
	Sheltered home	1.07 (0.59-1.99)	1.37 (0.62-3.03)	3.03 (0.72-2.76)	-	-	-
	Institution	0.85 (0.25-2.87)	-	4.81 (0.41-6.40)	-	-	-

Table 5.7 Sociodemographic predictors of depression after stroke

* p<0.05, ** p<0.01

	Time (yeas after stroke)					
	1	3	6	9	12	15
Depression pre-stroke	1.51 (0.93-2.46)	1.56 (0.90-2.70)	1.22 (0.56-2.67)	0.86 (0.35-2.10)	0.93 (0.29-3.00)	-
Treatment for depression pre-stroke	1.50 (0.91-2.49)	1.45 (0.81-2.60)	2.18 (0.96-4.98)	3.28 (0.75-14.30)	0.51 (0.05-4.89)	-
Smoking Never	1	1	1	1	1	1
Ex-smoker	1.10 (0.79-1.55)	1.35 (0.95-1.93)	1.24 (0.75-2.06)	1.77 (0.87-3.63)	2.53 (0.79-8.07)	0.28 (0.007-8.15)
Current smoker	1.10 (0.80-1.52)	1.64 (1.17-2.30)**	2.00 (1.29-3.13)**	1.86 (1.00-3.44)*	1.93 (0.62-6.06)	0.36 (0.004-28.0)
Drinks alcohol	0.87 (0.65-1.15)	1.24 (0.91-1.68)	1.08 (0.71-1.65)	1.07 (0.60-1.94)	1.62 (0.47-5.57)	-
Diabetes pre-stroke	1.01 (0.73-1.41)	1.32 (0.94-1.86)	1.25 (0.78-2.01)	1.16 (0.57-2.34)	1.31 (0.34-4.96)	-
Ischaemic heart disease pre-stroke	1.16 (0.82-1.65)	1.24 (0.88-1.75)	0.65 (0.38-1.10)	2.91 (1.37-6.19) **	2.00 (0.62-6.37)	5.88 (0.14-253.48)

Table 5.8 Risk factors predictors of depression after stroke

* p<0.05, ** p<0.01

	Time (Years after stroke)					
	1	3	6	9	12	15
Depression 3months after stroke	5.04 (3.55-7.16) **	4.07 (2.67-6.18) **	2.90 (1.61-5.22) **	4.98 (1.76-14.13) **	3.03 (0.55-16.57)	-
Anxiety 3 months after stroke	3.09 (2.19-4.36) **	3.14 (2.08-4.7) **	2.53 (1.42-4.51) **	2.30 (0.86-6.14)	3.46 (0.67-17.71)	-

Table 5.9 Depression and anxiety at 3 months after stroke predictors of depression in the long term

* p<0.05, ** p<0.01

	Time (years after stroke)					
	1	3	6	9	12	15
GCS 3-8	1	1	1	1	1	1
9-12	0.61 (0.27-1.35)	0.81 (0.37-1.80)	1.18 (0.35-3.94)	3.91 (0.77-19.95)	0.26 (0.03-2.20)	-
13-15	0.40 (0.21-0.77) **	0.69 (0.36-1.33)	1.07 (0.40-2.86)	2.30 (0.61-8.59)	0.28 (0.05-1.46)	-
Fail Swallowing test	1.56 (1.15-2.11) **	1.59 (1.16-2.18) **	1.20 (0.77-1.88)	0.84 (0.44-1.59)	2.60 (1.04-6.49) *	-
Urinary Incontinence	1.76 (1.33-2.34) **	1.36 (1.01-1.83) *	0.84 (0.52-1.37)	1.21 (0.64-2.31)	2.11 (0.84-5.28)	-
Visual field defect	1.45 (1.03-2.04) *	1.18 (0.85-1.65)	1.09 (0.68-1.75)	0.82 (0.41-1.67)	3.42 (0.96-12.15)	-
Neglect	2.22 (1.63-3.04) **	1.25 (0.90-1.74)	1.06 (0.64-1.76)	1.42 (0.70-2.90)	71.9(1.97-26.12)**	-
Dysphasia	1.13 (0.82-1.56)	1.05 (0.77-1.43)	0.86 (0.56-1.34)	1.23 (0.70-2.15)	0.98 (0.38-2.54)	-
Paresis	2.19 (1.59-3.02)**	1.22 (0.91-1.63)	1.97 (1.31-2.99)**	2.07 (1.20-3.56)**	2.60 (0.93-7.21)	0.19 (0.003-9.05)
Barthel index 7 d post-stroke	1	1	1	1	1	1
Severely disable	0.61 (0.43-0.87)**	1.11 (0.77-1.59)	0.93 (0.55-1.57)	0.94 (0.45-1.97)	1.25 (0.42-3.70)	-
Moderately disable	0.40 (0.29-0.55)**	0.52 (0.37-0.73)**	0.46 (0.30-0.73)**	0.49 (0.26-0.90)*	0.50 (0.19-1.34)	-
Independent						
Impaired Cognitive level	2.03 (1.47-2.81)**	1.60 (1.13-2.29)**	2.44 (1.44-4.15)**	1.54 (0.72-3.27)	0.69 (0.24-2.01)	-

Table 5.10 Stroke severity measures predictive of depression

* $p<0.05$ ** $p<0.01$

As detailed in the methods section, at certain time points some variables had 15 to 25% missing data. Table 5.11 shows ORs and CIs of variables analysed with and without multiple imputation.

Outcome	Exposure	OR and CI obtained on non imputed data	OR and CIs obtained on imputed data
Depression in year 1	Visual field defect	1.45 (1.03-2.04)*	1.46 (1.04-2.05)*
Depression in year 3	Barthel score 0-14	1	1
	Barthel score 15-19	1.11 (0.77-1.59)	1.06 (0.74-1.53)
	Barthel score 20	0.52 (0.37-0.73)**	0.54 (0.38-0.76)**
Depression in year 6	Living home alone pre stroke	1	1
	Living home with others pre stroke	1.08 (0.69-1.71)	1.09 (0.70-1.71)
	Sheltered home pre stroke	3.03 (0.72-2.76)	2.87 (0.74-11.14)
	Institutionalised pre-stroke	4.81 (0.41-6.40)	3.92 (0.30-50.48)
	Treatment for depression pre stroke	2.18 (0.96-4.98)	2.24 (0.99-5.05)
	Barthel Score 0-14	1	1
	Barthel score 15-19	0.93 (0.55-1.57)	0.92 (0.54-1.55)
	Barthel score 20	0.46 (0.30-0.73)**	0.43 (0.28-0.68)**
Depression in year 9	Treatment for depression pre stroke	3.28 (0.75-14.30)	2.66 (0.61-11.55)
	Barthel score 0-14	1	1
	Barthel score 15-19	0.94 (0.45-1.97)	1.02 (0.48-2.16)
	Barthel score 20	0.49 (0.26-0.90)*	0.56 (0.30-1.04)

Table 5.11 Predictors of depression after stroke. Comparison of results obtained with and without multiple imputations

* $p<0.05$, ** $p<0.01$

In most cases results obtained with MI were not significantly different from the ones obtained using a category for missing data. The association between Barthel score 20, showing independence for activities of daily living, and depression in year nine became not significant after using multiple imputation. Despite the change in statistical significance in one of the estimates, the difference between results was very small and of little clinical meaning.

5.4.2 Predictors of depression at any time point

All the sociodemographic variables, except living condition pre-stroke, were associated with depression at any time point in the univariate analysis. Among the clinical variables investigated, smoking and drinking habit pre-stroke, amount of alcohol consumed per week, diabetes pre-stroke, ischaemic heart disease pre-stroke, GCS score, visual defects, dysarthria, cerebellar symptoms and stroke subtype were not associated with depression at any time point in the univariate analysis. All the other variables were associated with depression at any time point in the univariate analysis.

Being unable to work, retired or unemployed, at baseline, and treatment for depression before stroke together with depression three months after stroke and anxiety three months after stroke are the main predictors of depression at any time point. Table 5.12 shows the ORs and CIs of the associations between sociodemographic, and clinical variables, and depression at any time point.

The OR and CI for the association between treatment for depression before stroke and depression at any time point after stroke showed no difference with the one calculated with MI (Table 5.13). Similarly the results of the initial analysis for the association between neglect and depression at any time point were not different from the MI analysis. Finally, when MI was used, the association between Barthel score and depression was not different from the original one.

		Depression at any time point OR (95%CI)
Age	<65	1
	>64	0.79 (0.66-0.94)**
Gender	M	1
	F	1.25 (1.05-1.48)*
Ethnicity	White	1
	Black	1.16 (0.95-1.43)
	Other	1.93 (1.33-2.78)**
Employment	Working	1
	Unemployed	1.71(1.03-2.82)*
	Unable to work	2.31(1.54-3.46)**
	Retired	1.76(1.32-2.35)**
	Student/Carer	1.45(0.79-2.67)
Social class	Non manual	1
	Manual	1.39 (1.15-1.68)**
Education level	No formal education	1
	Primary	0.63 (0.15-2.62)
	Secondary	0.33 (0.88-1.25)
	Tertiary	0.19 (0.05-0.80)*
Depression pre-stroke		1.62 (1.12-2.35)*
Treatment for depression pre-stroke		2.00 (1.33-2.99)**
Depression 3months after stroke		3.41 (2.51-4.62)**
Anxiety 3 months after stroke		2.96 (2.12-3.86)**
Fail Swallowing test		1.46 (1.17-1.81)**
Urinary Incontinence		1.51 (1.24-1.84)**
Neglect		1.53 (1.20-1.94)**
Dysphasia		1.30 (1.04-1.62)*
Paresis		1.73 (1.41-2.13)**
Barthel index 7 days post-stroke	0-14	1
	15-19	0.92 (0.71-1.18)
	20	0.47 (0.38-0.59)**
Impaired Cognitive level		1.53 (1.21-1.94)**

Table 5.12 Predictors of depression at any time point

* p<0.05, ** p<0.01

.	OR (95% CI)	OR (95%CI) MI analysis
Treatment for depression pre-stroke	2.00 (1.33-2.99)**	2.00 (1.34-3.00)**
Neglect	1.53 (1.20-1.94)**	1.48 (1.20-1.94)**
Barthel score 7 days post-stroke	1	1
0-14		
15-19	0.92 (0.71-1.18)	0.89 (0.69-1.14)
20	0.47 (0.38-0.59)**	0.50(0.40-0.61)**

Table 5.13 Predictors of depression at any time point. Comparison between results obtained with and without MI.

* p<0.05, ** p<0.01

5.4.3 Predictors of time after stroke of depression onset

58.9% (n=361) of the patients with depression at any time point, assessed at three months, were depressed at three months.

The only variables associated in univariate analysis with onset of depression at three months were not drinking alcohol pre-stroke, amount of alcohol consumed per week, dysphagia, urinary incontinence and paresis at baseline. These associations were still significant after adjusting for age, sex and ethnicity, except the association between not drinking alcohol and onset of depression. Patients drinking less than 14 units of alcohol per week had reduced risk of having depression at three months compared with patients not drinking any alcohol at all OR: 0.64(0.42-0.96) p=0.034. Consumption of other amounts of alcohol was not associated with depression starting at three months. Patients with dysphagia at baseline had increased risk of depression starting at three months compared with patients without dysphagia OR: 1.71 (1.14-2.56) p=0.009. Patients with incontinence had increased risk of depression starting at three months OR: 1.60 (1.10-2.31) p=0.013. Patients with paresis at baseline also had increased risk of depression starting at three months OR: 1.64 (1.09-2.45) p=0.016. No significant interactions were identified.

5.4.4 Predictors of duration of depression

50% (n=116) of the patients depressed at three months, assessed at one year had recovered from depression.

The only variable associated in univariate analysis with depression lasting more than a year was dependence for activities of daily living at baseline. The association was still significant after adjusting for age, sex and ethnicity. Patients with mild disability (Barthel Index 15-19) were less likely to have long lasting depression than those with severe disability OR: 0.32 (0.16-0.65) p=0.002. No significant interactions were identified.

5.4.5 Predictors of recurrent depression

Among the patients who were alive in year two, with incident depression observed at any time point, who had got at least three assessments, 56.2% (n=203) had recurrent depression.

Only two baseline variables were associated with recurrent depression in univariate analysis. GCS over eight was associated with lower risk, and neglect was associated with a higher risk of recurrent depression. Both associations were still significant after adjusting for age, gender and ethnicity. Compared with patients with GCS three to eight, patients with GCS nine to twelve had lower risk of recurrent depression OR: 0.08 (0.009-0.76) p=0.027, and patients with GCS above twelve OR: 0.12 (0.01-0.98) p=0.048. Patients with neglect at baseline had higher risk of recurrent depression OR: 2.12 (1.15-3.91) p=0.016.

5.4.6 Profile of patients at high risk of depression

Female patients under 65, not working at the time of stroke, of manual social class, no formal education, severe stroke and previous history of depression seem to be the group at higher risk of depression at any time point after stroke. Amongst the predictors identified only

inability to work, treatment for depression before stroke, Barthel score 0-14 at baseline, depression three months after stroke, and anxiety three months after stroke, showed more than two fold increased risk of depression. However, there were only few patients in the register showing these predictors simultaneously. There were only nine patients assessed for depression, with treatment for depression before stroke, unable to work at the time of stroke, and Barthel score 0 to 14. All of them had depression at some point of the follow-up. Another 55 patients had treatment for depression before stroke and Barthel score 0 to 14. The risk of depression at any time point for them was 76.4%. And finally 1365 patients had inability to work before stroke and Barthel score 0 to 14, of which 60.7% had depression at some point.

5.4.7 Profile of patients at low risk of depression

The results of this analysis also allow to define the profile of the patient at lower risk of depression: male patient, over 64 years of age, of non manual social class, tertiary education, no medical history of, or treatment for, depression pre-stroke, working at the time of stroke, intact cognitive level, absence of stroke severity measures (dysphagia, incontinence, neglect, dysphasia, paresis) and Barthel score of 20 seven days after stroke. There were no patients with this profile in the register. The risk of depression was calculated dropping one by one all these variables. The variables that could be dropped without raising the risk of depression over 15% (risk in general population) were gender, social class, education, medical history or treatment for depression pre-stroke, intact cognitive level, and stroke severity measures. Therefore the profile of the stroke patients in which the risk of depression at any time point is lower than the one in general population is: patients over 65, working at the time of stroke, with Barthel score of 20 seven days after stroke. There were 20 patients observed with this profile of which only one (5%) had depression at some point time point after stroke.

5.4.8 Variables observed at follow-up associated with depression 1, 3, 6, 9, 12 and 15 years after stroke

All the variables investigated in the univariate analysis as potential associations were significantly associated with depression in at least one time point. In the multivariate analysis disability, not drinking alcohol, particularly not drinking 1 to 14 units a week, not having any one to turn to, not seeing relatives enough, not seeing friends enough, low level of activity, anxiety and cognitive impairment at follow-up, had significant association in at least three time points. Living in an institution, living alone, being unemployed or retired and smoking at follow-up are also associated with depression. The ORs and 95% CIs of the associations between depression at 1, 3, 6, 9, 12 and 15 years after stroke and follow-up variables, adjusted by age, sex and ethnicity are presented in tables 5.14 and 5.15. Not significant interactions were identified in the analysis of associations.

Variables with 15 to 25% missing data were re-analysed as potential associations of depression at different time points using multiple imputation. Results obtained with multiple imputations did not have significant difference with the ones observed in the complete case analysis.

		Time (years after stroke)					
		1y	3y	6y	9y	12y	15y
Living circumstances	Private house alone	1	1	1	1	1	1
	Private house with other	0.83(0.62-1.12)	0.56(0.41-0.75)**	0.97(0.64-1.46)	0.69(0.40-1.2)	0.55(0.20-1.51)	-
	Institution	2.03(1.38-2.99**	1.18(0.80-1.74)	1.71(0.97-3.04)	1.05(0.48-2.29)	1.62(0.52-5.09)	-
	Other	1.67(0.43-6.54)	0.21(0.02-1.79)	5.99(0.52-68.3)	0.76(0.06-8.97)	-	-
Employment	Working	1	1	1	1	1	1
	Unemployed	3.93(1.12-13.82)*	1.68(0.90-3.14)	0.82(0.39-1.73)	2.28(0.72-7.16)	0.46(0.10-2.11)	1.32(0.03-60.42)
	Unable	7.60(3.55-16.24)**	3.12(1.79-5.43)**	1.51(0.74-3.09)	3.37(1.02-11.14)	0.42(0.05-3.35)	-
	Retired	3.04(1.43-6.46)**	1.80(1.06-3.06)*	1.14(0.61-2.14)	2.53(0.84-7.60)	0.41(0.08-2.05)	-
	Carer	1.00(0.10-9.64)	5.92(0.50-70.13)	-	-	-	-
Have someone to turn to	Yes	1	1	1	1	1	1
	No	2.76(1.54-4.94)**	4.51(2.38-8.54)**	3.31(1.59-6.88)**	3.67(1.18-11.44)*	2.42(0.44-13.37)	-
Sees relatives enough	Yes	1	1	1	1	1	1
	No	2.63(1.95-3.53)**	2.73(2.03-3.67)**	0.89(0.09-8.69)	4.40(2.48-7.80)**	2.26(0.85-6.01)	-
	Don't have any	2.62(1.22-5.63)*	4.00(1.58-10.12)**	2.39(0.24-23.71)	0.67(0.07-6.31)	2.38(0.13-43.74)	-
Sees friends enough	Yes	1	1	1	1	1	1
	No	3.55(2.62-4.81)**	3.69(2.71-5.02)**	0.68(0.07-6.71)	5.20(2.93-9.28)**	3.19(1.18-8.56)*	-
	Don't have any	1.69(0.92-3.08)	2.41(1.38-4.20)**	3.12(0.31-31.02)	4.16(1.18-14.70)*	-	-

Table 5.14 Sociological associations of depression after stroke

* p<0.05, ** p<0.01

		Time (years after stroke)					
		1y	3y	6y	9y	12y	15y
Smoking status	No	1	1	1	1	1	1
	Yes	0.95(0.71-1.27)	1.32(0.98-1.79)	1.83(1.20-2.80)**	1.81(0.99-3.29)	1.39(0.48-4.02)	0.80(0.02-38.7)
Drink alcohol	No	1	1	1	1	1	1
	Yes	0.56(0.43-0.73)**	0.53(0.41-0.70)**	0.52(0.36-0.76)**	0.52(0.32-0.87)**	0.24(0.9-0.61)**	3.64(0.05-251.61)
Alcohol intake (Units/week)	None	1	1	1	-	1	1
	<1	0.50 (0.36-0.69)**	0.54(0.40-0.72)**	0.61 (0.39-0.96)*	-	0.22(0.06-0.76)*	-
	<14	0.52 (0.26-1.02)	0.60 (0.31-1.14)	0.28 (0.10-0.76)*	-	0.52(0.04-6.45)	-
	14-21	0.53 (0.29-0.95)*	0.48(0.24-0.96)*	1.58(0.66-3.81)	-	1.04(0.006-18.82)	-
	>21	1.23(0.51-2.99)	3.37(0.60-19.00)	0.37(0.10-1.34)	-	-	-
	Unknown amount	-	-	-	-	-	-
Barthel score	Severe disability	1	1	1	1	1	1
	Mild disability	0.43 (0.31-0.61)**	0.58 (0.40-0.82)**	0.49(0.30-0.80)**	0.63(0.32-1.21)	0.24(0.08-0.73)*	0.40 (0.01-16.55)
	Independence	0.19 (0.13-0.27)**	0.17(0.12-0.25)**	0.17(0.10-0.29)**	0.17(0.09-0.36)**	0.11(0.03-0.36)**	-
Frenchay activity level	Inactive	1	1	1	1	1	1
	Moderately active	0.33(0.25-0.45)**	0.35(0.25-0.48)**	0.48(0.32-0.71)**	0.37(0.21-0.66)**	0.15(0.04-0.52)**	-
	Active	0.10(0.06-0.17)**	0.13(0.08-0.21)**	0.15(0.08-0.30**	0.04(0.01-0.14)**	0.07(0.01-0.62)*	-
Anxiety		8.49(6.36-11.35)**	8.38(6.21-11.31)**	8.44(5.59-12.74)**	14.94(8.03-27.79)**	15.93(5.82-43.63)**	-
Cognitive impairment		2.03(1.46-2.83)**	1.81(1.28-2.58)**	2.81(1.75-4.51)**	4.27(2.14-8.52)**	1.67(0.45-6.22)	-

Table 5.15 Clinical associations of depression after stroke

* p<0.05 ** p<0.01

Outcome	Exposure	OR and CI obtained on non imputed data	OR and CIs obtained on imputed data
Depression in year 6	Impaired cognitive level	2.81(1.75-4.51)**	2.78(1.70-4.51)**
Depression in year 9	Impaired cognitive level	4.27(2.14-8.52)**	4.11 (2.06-8.18)**
Depression in year 12	Frenchay score 0-15	1	1
	Frenchay score 16-30	0.15(0.04-0.52)**	0.15 (0.04-0.49)**
	Frenchay score 31-45	0.07(0.01-0.62)*	0.07 (0.008-0.58)**

Table 5.16 Associations of depression after stroke. Comparison of ORs and CIs obtained with and without multiple imputation.

* $p<0.05$, ** $p<0.01$

5.5 DISCUSSION

Depression at three months of stroke is the predictor most consistently associated with depression in the long term. Having disability at baseline consistently predicted a higher risk of depression. Anxiety three months after stroke, inability to work pre-stroke, being a smoker at baseline, and stroke severity were also predictors of depression. At follow-up, disability, low level of activity, not drinking alcohol, poor social networks and cognitive impairment were the variables most consistently associated with depression. In the analysis of predictors of depression at any time point, depression shortly after stroke and having no formal education compared with tertiary education, were the main predictors of depression. Stroke severity measures were also relevant predictors of depression at any time during the follow-up, depression starting early after stroke and recurrence of depression. Patients over 65, working at the time of stroke and independent for activities of daily living at baseline had an overall lower risk of depression, while patients unemployed at the time of stroke, disable at

baseline and with depression and/or anxiety shortly after stroke had a higher risk of having depression at some point during the follow-up.

5.5.1 Predictors and associations of depression

Disability both at baseline and at follow-up and low activity level at follow-up showed strong association with depression. Similar associations were observed previously[98 105 165] It has been reported that the scale used to measure disability (BI) has a ceiling effect and does not provide accurate assessments on patients with very severe disability.[199] Therefore, in very disabled patients the association between depression and disability may be stronger than the one observed. Patients active at follow-up were approximately ten times less likely to be depressed than those who are inactive. It was noted that some male patients score lower in the activity scale (FAI) not only because of their disability but because of the role they have in their families. However, the association between inactivity and depression was observed after adjusting for gender. Inactivity was the variable with the strongest association with depression. Inactive patients should be particularly considered for their high risk of depression after stroke.

Stroke severity, assessed by GCS, paresis, incontinence and other clinical variables, was a strong predictor of depression. Although some stroke severity measures like dysphagia were associated with depression up to 12 years after stroke, the associations were more consistent in the first three years of follow-up. Patients may become depressed shortly after stroke due to the experience of a life threatening event and its treatment. In the medium and long term, other variables like disability and isolation may be more relevant.[79] For the analysis of the association between stroke severity and depression having data on the National Institute of Health Stroke Score (NIHSS)[205] would have been ideal. This scale provides a very reliable and intuitive value for stroke severity.[206] The case mix variables included in the models were

chosen for their clinical relevance and their prognostic value,[207 208] and therefore provide informative estimates on the association between stroke severity and depression. The association between stroke severity and depression may be explained by the overall impact that a severe stroke has on patients and their families. Stroke severity is not a variable reflecting only biological changes. However, the association between severity and depression would also support the hypothesis of the direct links between neurological damage and depression.[264] A previous systematic review of depression and stroke lesion location concluded that the evidence did not support the risk of depression after stroke being affected by the location of the brain lesion.[190] The results of the literature review presented in Chapter two did not show a consistent association between depression and neurological damage, including stroke location, stroke size and stroke subtype. A severe stroke is a negative life event that puts the patient at risk of depression.[177 265] This psychological effect, and not the neurological damage, may explain the association between stroke severity and depression. Stroke severity is in any case a predictor of clinical value, as it makes patients at high risk of depression identifiable right from the acute phase.

The association between cognitive impairment and depression has been reported previously.[99] The associations between cognitive impairment, disability and depression are very complex as each of the three can be cause and or effect of the other.[62 63] The association between disability and both cognitive impairment and depression may explain partly the association between depression and cognitive impairment. It has been reported that patients of lower educational attainment and older age may score lower in the cognition tests.[209] The associations between cognitive impairment and depression were observed after adjusting for age. However, they may still be an overestimation in patients with low level of education.

Depression, and treatment for depression, before stroke were associated with depression at some point during the follow-up although no specific time points for this association were identified. A past medical history of depression may not be very relevant during the clinical management of a patient at the time of stroke. These data of past medical history may not have been accurately recorded in the medical notes and therefore it may not have been collected by the SLSR. It is possible that some patients who were depressed at some point before stroke may have been categorised as not having past medical history of depression. This would have led to an underestimation of the association between depression before stroke and after stroke. A systematic review of the predictors of depression after stroke reported no evidence of association between depression before stroke and depression after stroke.[62] The differences in methods, sample size or time to follow-up may explain the difference between the previous studies and the results of this thesis. The aetiology of depression remains unclear.[31] Factors such as biochemical disorders, genetics or personality, which may be involved in the aetiology of depression before stroke, are still present after the event and they may explain why depression before stroke in this dataset is associated with depression after stroke.

A high long term risk of depression amongst patients depressed three months after stroke was also observed. Interventions targeting patients depressed at three months should consider the long term prognosis of depression shortly after stroke. The association between anxiety at three months and depression in the long term may be explained by the strong association between anxiety and depression all along the follow-up. The risk of depression in patients with anxiety in general population is well documented.[266] Traditional diagnostic and treatment approaches have used a hierarchical approach with depressive symptoms taking preference. Furthermore, some argue that certain forms of anxiety should be conceptualised as a residual or severity marker of depression.[267] However, factor analysis has found that

anxiety and depression appear to be distinct [266 268 269] and differential response to treatment between the two conditions has been observed.[270] In any case anxiety may be a clinical sign easy to recognise, alerting the clinician about the high risk of depression in the long term.

Inability to work or being unemployed before stroke and at follow-up showed an association with depression. That was an expected result as patients with disability have a well reported high risk of depression.[271 272] Up to 60% of patients in this study were under 65 years of age, the traditional age for retirement. Fear of economic stability, loss of job or job dissatisfaction have been previously reported as being associated with depression after stroke.[273]

An association was observed between social isolation and depression. As described in chapter three, this variable was assessed with two non validated questions. However, these observations are very plausible. The association between isolation and depression in stroke patients, and in patients with other health conditions, have been reported previously[62 98 274-276]. The negative impact that social isolation has on general health[194 195] may play a role in its association with depression after stroke.

The association between not drinking alcohol and depression was consistent during the follow-up. This association was especially consistent in patients drinking less than one unit a week. A lower risk of depression was identified also in a fewer number of time points for patients drinking one to 21 units a week, and no associations were found between drinking between more than 21 units a week (excessive drinking)[277] and depression. These associations remained unchanged after adjusting for family and friends support. It seems that the association between drinking a low amount of alcohol and lower risk of depression is independent of the social behaviour. These results have to be interpreted with caution. Alcohol drinking behaviour is a major concern in clinical medicine and public health.[277] A recent systematic review showed a strong association between drinking alcohol excessively

and depression in general population.[23] Our results did not show association between drinking over 21 units a week and depression. The case of stroke patients may be different from general population, or maybe the low number of SLSR patients in these categories (n<77) did not give statistical power enough to show the association. Many studies have investigated the association between excessive alcohol intake and depression[23]. The effect of moderate drinking on mental health outcomes may be investigated in future studies to confirm if low amounts of alcohol have a beneficial effect on mental health similar to the one observed on cardiovascular outcomes.[278] It should also be mentioned that participants may not have reported their drinking habits truthfully. The lower response to epidemiological questionnaires that have sensitive items has been observed before.[213] A large number of patients who drink heavily, reporting not to drink, could explain these results.

Female patients had a higher risk of depression at two points of the follow-up. Most of the studies included in the systematic review presented in Chapter two found a higher risk of depression in women, although the difference was not statistically significant in most cases. In the general population the prevalence of depression is higher in women.[279] Two large epidemiological studies found, OR: 1.7[15] and 2.0[16] for women compared to men. This thesis observed higher risk in women only at one and three years after stroke, and the ORs were 1.29 and 1.41. The OR for depression in women observed during the whole follow-up period was 1.25. Stroke and its consequences reduce the difference in risk of depression between women and men although some difference can still be observed. Previous studies may not have had enough statistical power to detect this.

Studies of the general population consistently show that the risk of depression is approximately two fold higher at ages younger than 60[16] or 65[15]. However, in this thesis patients aged under 65 only had lower risk of depression at one time point. When the risk

over the whole follow-up was calculated the OR was 1.26 for patients under 65 compared to patients 65 or over. Stroke seems to be more relevant as an aetiological factor for depression than the other factors that lead to higher risk in younger individuals from general population. Therefore, after stroke age becomes a less important predictor of depression.

Ischaemic heart disease pre stroke only predicted depression at nine years of stroke. Diabetes did not predict depression at any time points. None of them was associated with a higher risk of depression during the follow-up time. The association between chronic diseases and depression that has been reported in general population[258] was not observed in this thesis. It seems that stroke and its consequences are more important factors for depression than other chronic diseases present prior to stroke.

The hypothesis suggesting that there are biological psychological and social factors involved in the aetiology of depression is widely accepted[19 31 279]. This thesis aimed mostly to investigate predictors of depression that could be useful in clinical medicine and public health. The role of biological factors such as stroke severity, psychological factors such as anxiety, and social factors such as social isolation, was observed. Most predictors were not purely biological, psychological or social, and in many cases there was strong colinearity amongst them.

There were a low number of variables predicting outcomes of the natural history of depression after stroke. The risk of depression at some point after stroke can be predicted with sociodemographic and clinical observations but the association of these variables with the natural history of depression is much weaker. Stroke severity measures predicted depression starting within three months of the acute event and an increased risk of recurrent depression. Disability predicted depression lasting more than a year. These results confirm the hypothesis that patients may become depressed at different times for different reasons,

with stroke severity being more relevant shortly after the acute event, and disability in the long term. The rest of observed variables showed no significant association with any outcomes of the natural history of depression after stroke.

5.5.2 Strengths and limitations

The population based register data and long follow-up provide some of the strengths of this analysis. The high statistical power derived from the large sample size allows building stable regression models of predictors even long after stroke, when mortality has reduced the cohort of patients importantly. This study of predictors has also been conducted according to accepted criteria[88], which includes minimisation of selection bias, assessment of mood with a validated tool, proper description of the statistical methods, adequate sample size, correct description of explanatory variables, inclusion of confounders in the models, reporting of ORs and CIs and production of clinically meaningful results. Hackett et al, in their systematic review of studies of predictors of depression after stroke, discussed that a previous history of depression could be included in the statistical models as a potential confounder. They also mentioned other potential confounders to be considered such as comorbidities, cognitive impairment (which may modify any psychological reaction), physical disability, social support or bereavement, as they are common amongst stroke survivors.[26] Since the election of confounders is a matter of judgement, this observation may be right. However, these variables may not only be confounders but variables in the causal pathway between the exposure and the outcome. The results of an analysis including these variables in the models would have been more difficult to interpret.

As discussed in chapter three, the estimation of clinical outcomes using scales has some limitations. Nonetheless, all scales have good performance and they allowed assessing a very large number of patients during a long follow-up, which would have been unfeasible

otherwise. The potential error introduced by each individual scale is acknowledged in the discussion of the different results.

The interpretation of these results should account for the possible residual and unmeasured confounding. When analysing epidemiological data, the true model is not known; the variables actually confounding the association of interest, the form in which they should enter the model, or the time scale over which they act are uncertain. It has been suggested that confounders can be identified by evaluating the change in the exposure-outcome estimate. For example, if the estimate adjusted for a variable differs by more than 15% from the estimate obtained without adjusting, the variable should be considered a confounder. However, strict adherence to such a rule could lead to true confounders' being disregarded. In this thesis, the variables included in the models were informed by the systematic review presented in chapter two. In some studies, confounders are omitted from the analysis because of missing data leading to loss of information. In this chapter this potential source of bias due to unmeasured confounding has been minimised using methods of dealing with missing data.[280]

The personal and technical resources involved to follow-up so many stroke patients for so long have been substantial. As all cohort studies, the SLSR has some missing data. It should be noted that an important reduction of the sample size during the follow-up is due to mortality and not to loss to follow-up. As presented in chapter four, there were little differences between sociodemographic characteristics of patients who were and those who were not assessed for depression. Up to ten years after stroke those who were not assessed tended to have more severe strokes. However, two different statistical methods have been used to remove the bias coming from the missing data: sensitivity analysis and MI, for the analysis of predictors with 15 to 25% missing data. MI was conducted under the assumption

that missing data was missing at random (MAR). The results of MI are quite consistent with the ones obtained without it. An important part of the missing data may be missing completely at random (MCAR), therefore not introducing bias. It could still be assumed that the possibility of being missing might be associated with not observed variables, which is a pattern of data missing not at random (MNAR). Probably this is the case for some of the missing data. However, it should be acknowledged that MI and complete case estimates were always consistent. This suggests that, while part of the sociodemographic groups are more likely to be missing than others, this had little impact on the estimates of predictors of depression after stroke.

An important limitation that could not be managed during the field work and neither during the statistical analysis is that some patients were unable to respond to the HAD questionnaire. Our analysis was restricted to patients with the outcome variable observed. The proportion of patients with severe strokes, cognitive impairment, and other variables predicting depression is higher amongst those not responding to HAD than in those who respond. The proportion of patients with depression may also be higher amongst those not responding to HAD. Therefore the bias could not be completely removed. The association between the predictors identified and depression may be stronger than what has been observed in this chapter, higher ORs. This is a limitation affecting most studies not only of depression after stroke but of depression in general.[79] Even in patients in whom depression was assessed, the assessments were done with a scale. Although the psychometric properties of HAD are good and the cut-off point used to identify cases of depression was the one recommended by a systematic review, ideally depression should be diagnosed with the DSM-IV criteria. The use of a scale was needed as the annual assessment of such a large number of patients with DSM-IV criteria would have been unfeasible.

5.5.3 Implications for clinical practice

This chapter shows that 60% of the patients with disability at baseline, who were unable to work at the time of stroke, had depression at some point. This profile of high risk is easy to identify for the clinician. The number of patients fitting this profile was large (1365). Interventions should focus in this particular group of survivors as the need for medical treatment for depression may be specially needed.

Patients over 65 years of age working at the time of the stroke, with no disability had lower risk of depression than the general population. However, the number of patients fitting these profiles is low. Most of these predictors were not present at the same time in the same patient. Therefore it remains difficult to describe a clinical profile for patients at low risk of depression which may not require interventions at all. Clinicians should still be aware of the overall high risk of depression after stroke even in patients not fitting the high risk profile, in both the short and the long term.

Depression can be screened with two questions: During the past month, have you often been bothered by feeling down, depressed, or hopeless? and During the past month, have you often been bothered by little interest or pleasure in doing things? If the response is "yes" to either question patients should be assessed further.[281] This very simple tool has 97% sensitivity and 67% specificity in adults.[282] Stroke physicians and GPs should be able to use the screening tool and also to use the DSM criteria[85 86], in case the screening indicates so, to make a formal diagnosis of depression. Since depression is so frequent after stroke, the time of highest risk is shortly after the acute event, and the screening tool is so simple, it could be suggested that all stroke patients are routinely screened for depression during the acute phase. After discharge patients should be screened periodically in the long term by the primary care team. The high risk of patients with inability to work before stroke and disability after stroke should

be acknowledged by clinicians. GPs and primary care nurses should also be aware not only of the baseline predictors but also the associations of depression that may be present at follow-up. It should be noted that the risk of depression decreases very significantly if a patient is not depressed shortly after stroke. Policy makers could consider the inclusion of this need for clinical action in the primary care guidelines.[283]

In order for these interventions to have a positive clinical effect, cooperation from patients and carers is required. Doctors must make sure that patients and carers understand that depression is likely to present shortly after stroke and that it can be approached medically. They have to know the symptoms of depression that should make them seek medical advice promptly. Finally, patients should know that most episodes of depression have relatively short duration.

5.5.4 Implications for future research

Since most interventions implemented so far were based on poor epidemiological evidence, it will be necessary to re-examine the benefits of screening, prevention and treatments when they are used at the time of maximum risk with the right patients.

Most predictors of depression are not only biological. These include unemployment, disability, low level of activity, not drinking alcohol and poor social networks. Other predictors, such as anxiety, depression shortly after stroke and cognitive impairment, have a biological component as well as a social and/or psychological one. However, the most common approach to treating depression is still antidepressants. In the future researchers should also consider a more complex approach that may have to be delivered in cooperation with professionals working outside the health service. These interventions may include group physical activity programmes, peer support groups, and behavioural couples' therapy.

Like in other areas of medicine, whether interventions are effective or not may depend on patients, carers and clinicians views, opinions and beliefs. Qualitative research studies on this area would help in the design and implementation of effective interventions.

CHAPTER 6: ASSOCIATIONS BETWEEN DEPRESSION IN THE FIRST YEAR AND OTHER HEALTH OUTCOMES UP TO 15 YEARS AFTER STROKE

6.1 ABSTRACT

Background: Evidence on the association between depression after stroke and other health outcomes in the long term is insufficient to understand the overall relevance of depression after stroke.

Objective: To investigate the association between depression in the first year after stroke and mortality, stroke recurrence, disability, cognitive impairment and quality of life up to 15 years after stroke.

Methods: Data from patients with first ever strokes registered in the population-based South London Stroke Register between January 1995 and December 2009 (N at registration=4022). Patients were followed up three months after stroke and then every year for up to 15 years. Follow-up included assessments for depression (Hospital Anxiety and Depression, depression subscales scores >7 = depression) disability (Barthel Index), cognition (Abbreviated memory test or Mini-mental estate examination), and health related quality of life (SF-12 or SF-36). Multivariable regression models were used to investigate the association between depression within a year of stroke and mortality, stroke recurrence, disability, cognitive impairment and quality of life up to 15 years after stroke. Models were adjusted for age, sex, ethnicity, stroke severity (Glasgow coma score, urine incontinence and hemiparesis) disability in the acute phase of stroke.

Results: Depression in the first year after stroke was associated with higher mortality up to 15 years after stroke. No significant association was identified between depression and stroke recurrence. Disability and cognitive impairment rates were also significantly higher

amongst patients depressed in the first year after stroke. Depression after stroke also showed a consistent association with lower quality of life at follow-up.

Conclusion: Depression is independently associated with negative health outcomes. These finding should be considered when assessing the clinical relevance of depression after stroke. Future interventions for depression after stroke may have an effect on these outcomes as well.

The analysis of outcomes of depression up to 15 years after stroke was presented as an oral presentation in the 2011 European Stroke Conference. (Appendix one)

A paper with the results presented in this chapter has been published in the Journal of Neurology, Neurosurgery and Psychiatry. (See appendix one)

6.2 INTRODUCTION

The analysis of the natural history of depression after stroke described on Chapter four shows that depression is a frequent, chronic and recurrent problem among long term stroke survivors. However, in order to understand the clinical impact of depression after stroke, it is also necessary to investigate the association between depression and other health outcomes in the long term.

The literature review included five studies reporting an association between depression and other health outcomes. Nonetheless, most of these studies had limitations including small sample size, short follow-up, and a poor description of the statistical methods used for the analysis. Therefore, the association between depression after stroke and other health outcomes remains poorly understood.

This Chapter will address the following question:

- What are the long term associations of depression after stroke?

6.2.1 Depression and mortality

The systematic review presented in Chapter two identified two studies where depression after stroke was associated with higher mortality[177 178] and a third one reporting no association between depression and mortality.[117] The two studies reporting that depression after stroke predicts higher mortality at follow-up had a sample sizes of 84[177] and 91[178]. They recorded whether patients were still alive 17 months, and 8 to 11 years after stroke respectively, and reported increased mortality amongst depressed patients with Odd Ratio (95%CI): 3.7 (1.1-12.2) and 8.1 (0.9-72.9). The study where depression after stroke did not predict higher mortality had a sample size of 163 and the data on mortality was collected 13 months after stroke. No numerical result was presented for this lack of association.[117] The description of

the methods in the three studies was very brief. The variables included in the predictive models were not reported, therefore it was not possible to know whether the statistical analysis had been conducted according to quality criteria.[88 198] It is difficult to interpret the inconsistency observed in these three studies. Their validity, and therefore the clinical implication, of these studies is unclear. The electronic search identified other studies including two of good quality, from which patients with haemorrhagic strokes had been excluded, observing an association between depression and mortality. The interpretation of these results was made with caution as the difference in the populations with the studies of unselected stroke patients was noted.[181 187]

Previously, higher mortality has been observed in patients with depression in the general population (not disease specific samples) [284 285] and also amongst patients with depression and other physical diseases including cancer,[286] diabetes[287] and ischaemic heart disease.[42] Depression after stroke has some similarities with depression in general population[15] such as the chronic recurrent course reported in the Chapter four of this thesis. It would be plausible that depression after stroke may be associated with increased mortality in the long term as opposed to a null hypothesis of no association between depression after stroke and mortality. Testing this hypothesis should provide evidence on the impact of depression in stroke patients and should help to develop effective interventions for it.

6.2.2 Depression and stroke recurrence

Patients surviving an initial stroke are known to be at significantly increased risk for further strokes compared to the general population.[288] An association between depression and an increased cardiovascular risk has been reported in a systematic review. However, the authors of this review noted that studies were very heterogeneous and therefore they recommended that the results of the meta-analysis should be interpreted with caution.[289] Two systematic

reviews reported an association between depression and a stroke specific increased risk.[289 290] In 2007 Van der Kooy and colleagues reported a pooled OR for patients with depression compared with those not depressed of 1.43 (1.17-1.75).[289] In 2011 Pan and colleagues reported pooled adjusted HRs of 1.45 (95% CI, 1.29-1.63) for total stroke, 1.55 (95% CI, 1.25-1.93) for fatal stroke, and 1.25 (95% CI, 1.11-1.40) for ischemic stroke.[290] Considering this evidence it could be hypothesized that depression after stroke may be associated with a higher rate of stroke recurrence. However, a previous study conducted with ten years follow-up data from the SLSR did not identify depression after stroke as a predictor of stroke recurrence.[291] In this study depression was included in a model with other potential predictors of recurrence and backward stepwise logistic regression was used. This statistical method has limitations, as there is a chance that the automated selection may not include all the clinically relevant variables, such as depression, in the final model.[292] The systematic review presented in Chapter two did not identify any other studies where patients had been assessed for depression after stroke and then for stroke recurrence at a later time point. In this chapter, using 15 years follow-up data from the SLSR, it will be tested whether depression after stroke predicts stroke recurrence or not.

6.2.3 Depression and disability

The association between depression and disability at a later time point has been documented in general population.[293] This association has also been observed in patients with other conditions such as chronic obstructive pulmonary disease, heart failure and diabetes.[294 295] However, most studies conducted in stroke patients have investigated disability as a predictor of depression, or as an association present at the same time. The systematic review conducted for this thesis identified one study of unselected stroke patients reporting that depression in the acute phase predicts disability one year after stroke.[179] Although the quality

of this paper was good according to accepted criteria,[88 198] it still had some limitations such a short follow-up. In any case the results coming from only one paper may not be enough to inform significant changes in clinical practice. A previous systematic review identified other studies reporting an association between depression after stroke and disability.[63] However, most studies in that review had some limitations including selection of patients of specific age groups and assessments for depression and disability at the same time point after stroke. The analysis presented in Chapter five showed that disability during the acute phase of stroke predicts depression at follow-up and also that disability and depression present simultaneously during the 15 years following a stroke. Whether or not depression after stroke is independently associated with disability at follow-up remains unclear.

6.2.4 Depression and cognitive impairment

Cognitive impairment has been widely reported in patients with depression in general population.[296] It has also been reported as an outcome of stroke.[259] However, the systematic review presented in Chapter two did not identify any studies of good quality where patients assessed for depression after stroke had been assessed for cognitive impairment at a later time point. The effect of depression in the cognitive status of stroke patients remains unknown.

6.2.5 Depression and quality of life

Two studies included in the literature review (Chapter two) identified depression after stroke as a predictor of lower quality of life one year after stroke.[179 180] However, only one of them described properly the methods used in the analysis.[179] The association between depression after stroke and the quality of life in the long term has not been investigated.

The evidence on the association between depression after stroke and quality of life, as well as the association between depression after stroke and mortality, stroke recurrence, disability, and cognitive impairment, is weak.

6.3 METHODS:

Data from patients registered in the SLSR between 1st January 1995 and 31st December 2009 (N at registration=4022) were used to address the question. Follow-up data from these patients, collected between the 1st April 1995 (first three months follow-up assessments) and the 31st August 2010, were used. The number of patients available for each follow-up has been presented in chapter four (Figure 4.1). Patients were registered during the acute phase of stroke and then they were followed up The methodology of the SLSR has been described in chapter three and is summarised below.

Assessments for depression were performed using the Hospital Anxiety and Depression scale (HAD).[214] Patients with a score > 7 in the depression subscale were considered to have depression.[218] HAD was routinely collected between 1997 and 2006. Patients registered in 1995 (n=299) were not assessed at three months and one year but they were assessed in subsequent follow-ups. Patients registered in 1996 (n=350) were not assessed at three months but they were assessed at subsequent follow-ups. Data on HAD was therefore not included from these patients in the respective estimates for early rates of depression. As HAD cannot be answered by proxy, no data could be collected from patients unable to respond to the questionnaire, which included patients who had a cognitive deficit, severe disability, communication difficulties or multiple comorbidities that the fieldworker judged such that the completion of the questionnaire would be invalid.

Disability was assessed at each follow-up with the Barthel index. [211 260] Scores of 0-14 were categorised as severe disability, 15-19 moderate disability, and 20 independent.

Cognitive function was also assessed at each follow-up with the Mini Mental State examination (MMSE)[209 259] except from the period between 2001 and 2006 when the Abbreviated Memory Test (AMT)[210] was used. Patients with MMSE score <24 or AMT Scores 0-7 were considered cognitively impaired.[209 210]

Quality of life (QoL) was assessed with the SF-36[226] between 1995 and the 29th of February 1999, and the SF-12[227] between the 1st of March 1999 and the 31st August 2010. Two domains of QoL were observed mental domain and physical domain. Scores collated from the scales ranged from 0 to 100 with high score representing better QoL.[226 227]

Mortality data was collected by the SLSR follow-up team or from the Office of National Statistics (ONS). An updated list was sent every six months to the Office for National Statistics of all patients who were alive or who were known to be deceased but for whom there was no death record. They informed the register of any patients that had died. Finally Death certificates from the Health Authority serving the SLSR population and post-mortem records from the local coroner's office were also searched every three months.

The same overlapping sources used by the SLSR to identify first ever strokes were used to identify recurrent strokes.

6.3.1 Statistical Methods:

The analysis of the natural history of depression after stroke, presented in Chapter four, showed that most patients have the first symptoms of depression within a year of stroke with less than 10% of patients presenting their first episode of depression after that time. In this chapter depression at three months and one year after stroke, or at either of these two time points, were used as the exposure variable in all the analyses. Mortality, stroke recurrence, disability, cognition and quality of life up to 15 years after stroke were the outcome variables.

The number of patients was higher in the first five years of follow-up, allowing for a much more stable regression models and higher statistical power, therefore the analysis focused on outcomes observed during this period. However, in order to make the best possible use of the long term data, and provide evidence on the long term impact of depression after stroke, associations between depression an outcomes observed after year five years of follow-up were also reported.

Table 6.1 shows the distribution of variables included in the models. These are sociodemographic and clinical variables measured at baseline, and depression during the first year after stroke.

The statistical methods needed to handle missing data on outcomes are computationally intensive and not routinely included in statistical software so they are not commonly applied.[232] Therefore, only patients with complete outcome data were included in the analysis. Most variables analysed as potential predictors had some missing data. A separate category was assigned to them e.g.: Paresis 0 (No), 1 (Yes), and 2 (Missing). Sensitivity analysis was conducted to compare estimates obtained in multivariate analysis when the category for missing data was included and when it was not included. Estimates of the analysis conducted with and without the missing data category are reported.

Univariate analyses, using Kaplan–Meier curves, log rank tests and Cox regression models, were used to test the association between depression at three months, one year, and at either of these two time points, and mortality up to 15 years after stroke. At a second stage, potential confounders, including case severity (GCS, incontinence and hemiparesis), together with disability at baseline, age, sex and ethnicity were included in the Cox models.[297-309]

		N (%)
Age	0-64	1248 (31.03)
	>64	2774 (68.97)
	Unknown	0
Gender	Male	2029 (50.45)
	Female	1993 (49.55)
	Unknown	0
Ethnicity	White	2889 (71.83)
	Black	805 (20.01)
	Other	225 (5.59)
	Unknown	103 (2.56)
G-C-S	3-8	652 (16.21)
	9-12	450 (11.19)
	13-15	2759 (68.60)
	Unknown	161 (4.00)
Paresis	No	714 (17.75)
	Yes	2724 (67.73)
	Unknown	584 (14.52)
Incontinence	No	2025 (50.35)
	Yes	1722 (42.81)
	Unknown	275 (6.84)
Barthel score	0-14	1775 (44.13)
	15-19	521 (12.95)
	20	763 (18.97)
	Unknown	963 (23.94)
Depression at 3 months	No	740 (25.02)
	Yes	361 (12.20)
	Unknown	1857 (62.78)
Depression at 1 year	No	876 (33.11)
	Yes	357 (13.49)
	Unknown	1413 (53.40)
Depression at either 3 months or 1 year	No	982 (34.9)
	Yes	602 (21.4)
	Unknown	1232 (43.7)

Table 6.1. Variables included in the models.

In a similar way, univariate analyses using Kaplan–Meier curves, log rank tests and Cox regression models were used to test the association between stroke recurrence up to 15 years after stroke in patients depressed and not depressed at three months, one year after stroke and at either of these two time points. At a second stage, potential confounders, including case

severity (GCS, incontinence and hemiparesis), together with disability at baseline, age, sex and ethnicity were included in the Cox models.[297-309]

Univariate multinomial logistic regression models were used to analyse the association between depression three months after stroke, one year after stroke, and at either of these two time points, and disability at follow-up. Then multivariate analyses were conducted in which models were adjusted for age, gender, ethnicity, stroke severity measures (GCS, Incontinence and hemiparesis) and disability at baseline. Data used in the analyses is presented in Appendix five.

The association between depression at three months, one year and either of these two time points, and cognitive impairment was analysed with univariate logistic regression. In a second stage models were adjusted for age, gender, ethnicity, stroke severity measures (GCS, incontinence and hemiparesis) and disability at baseline. Data used in these analyses are presented in Appendix six

Univariate linear regression models were used to investigate the association between depression at three months, one year and either of these two time points and quality of life at follow-up. Then models were adjusted for age, gender, ethnicity, stroke severity measures (GCS, incontinence and hemiparesis) and disability at baseline. Data used in these analyses is presented in Appendices seven and eight.

The multivariate statistical models were built, in the analyses of outcomes following guidelines for prospective studies in stroke cohorts: The regression method was chosen depending on the outcome. Important potential confounders were included in the models. [74] [185] The models intended to be useful in clinical practice, they were therefore predictive models (aiming to calculate the probability that an event occurring) and only included readily available pre-stroke and acute stroke variables. The sample size was adequate to build the

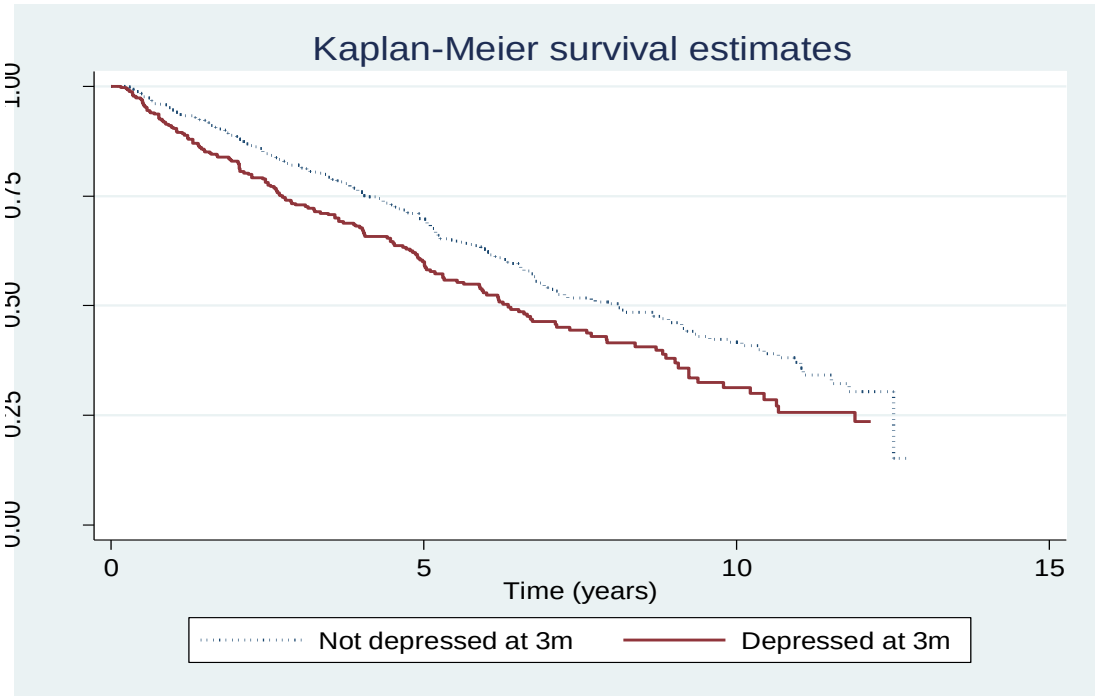
model and when the sample size introduced any limitations it was reported. The number of cases with the outcome of interest and the total number of cases in the sample were reported.[74 185] All independent variables have been clearly described, including when each variable was measured, how it was measured and coded, and in what form it was entered into the model. There was also an adequate number of people with each risk factor for the model. Automated methods, which can select data only for being statistically significant rather that clinically meaningful, were not used. Reporting the usefulness of the model included 95% confidence intervals around odds ratios. Interaction terms for age and Barthel score, were included in all the multivariate models.[26 88]

6.4 RESULTS:

6.4.1 Depression and mortality

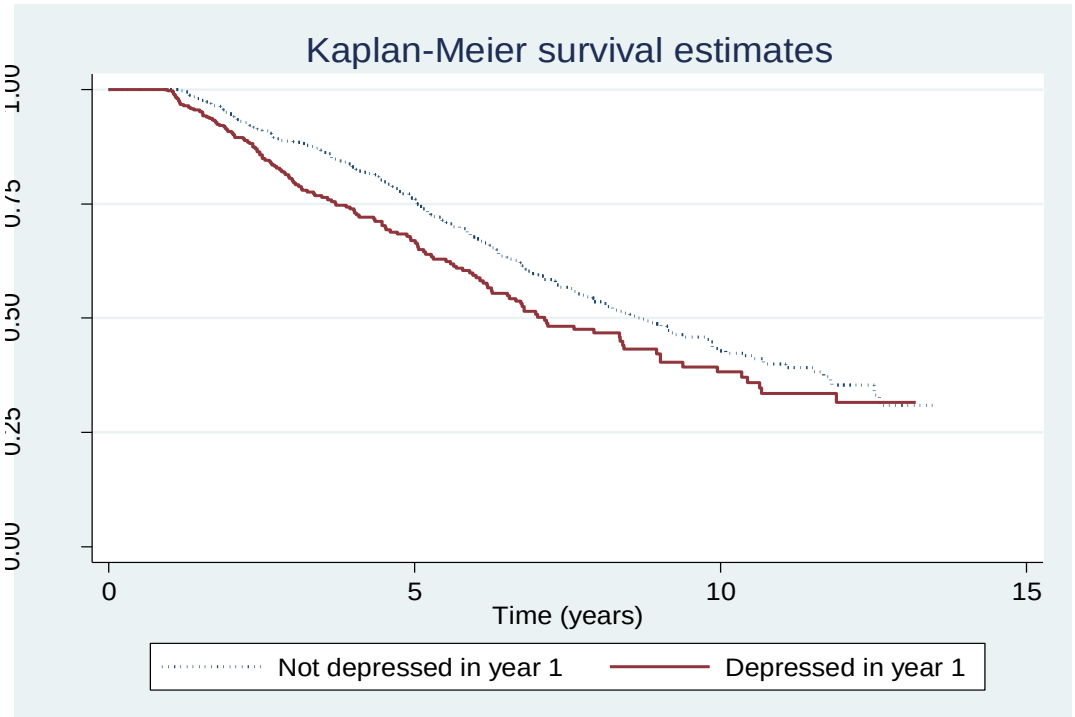
In the 15 years of follow-up death was reported in 1448 patients who were alive at three months and 1136 patients alive at one year. The mortality rate was higher for patients who were depressed at three months, one year or at either of these two time points in the univariate analyses. Figures 6.1, 6.2 and 6.3 show the Kaplan-Meir survival curves, and the results of log rank tests, for these associations.

In the adjusted analysis, depression at three months, depression in the first year and depression during year one were still associated with higher mortality. However, when the analysis was conducted with patients with complete data only, the evidence of association between depression at one year and mortality became weaker HR: 1.22 (0.98-1.54). Tables 6.2 and 6.3 show the Hazard ratios for these associations for multivariate analysis conducted with and without missing data categories.



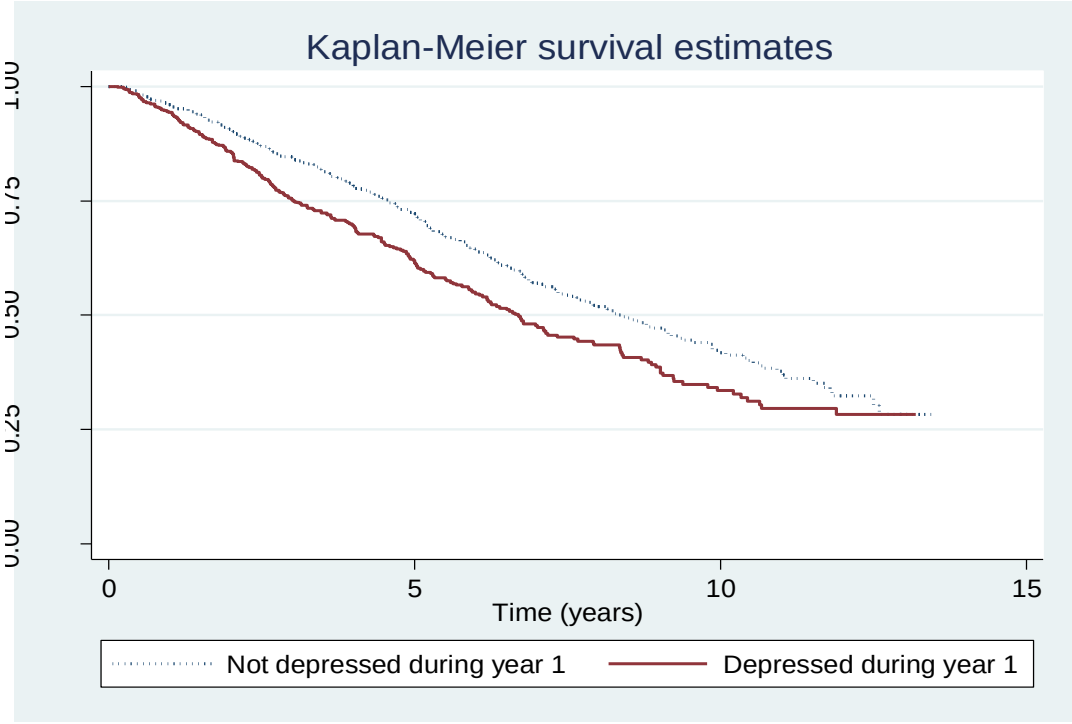
Log rank test p=0.0031

Figure 6.1 Survival of patients by depression state at 3 months



Log rank test p=0.0102

Figure 6.2 Survival by depression state at 1 year



Log rank test p=0.0012

Figure 6.3 Survival state by depression state during year 1 (depressed at either 3 months or 1 year)

	Hazard ratio	CI	p
Depressed at 3 months	1.25	1.03-1.53	0.023
Depressed at 1 year	1.25	1.02-1.54	0.029
Depressed during year 1	1.25	1.06-1.47	0.007

Table 6.2 Mortality at follow-up of patients depressed at different time points. Multivariate analysis. Category for missing data included.

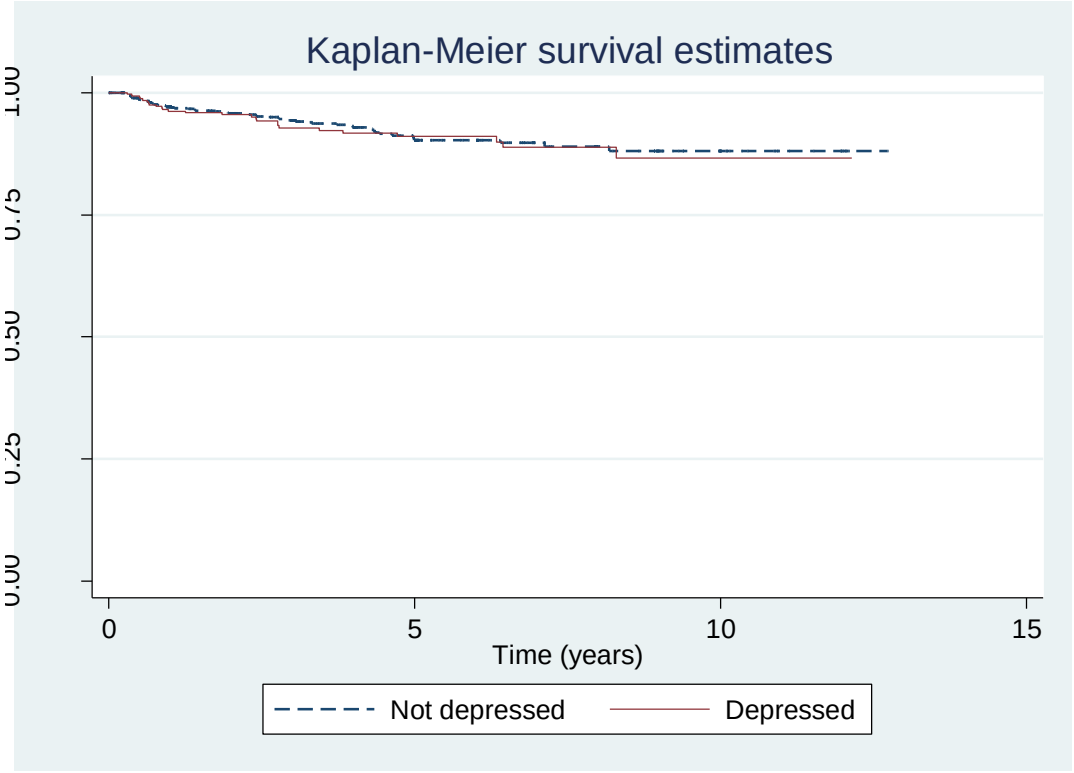
	Hazard ratio	CI	p
Depressed at 3 months	1.37	1.08-1.73	0.009
Depressed at 1 year	1.22	0.98-1.54	0.080
Depressed during year 1	1.34	1.11-1.62	0.002

Table 6.3 Mortality at follow-up of patients depressed at different time points. Multivariate analysis for patients with complete data only.

6.4.2 Depression and stroke recurrence

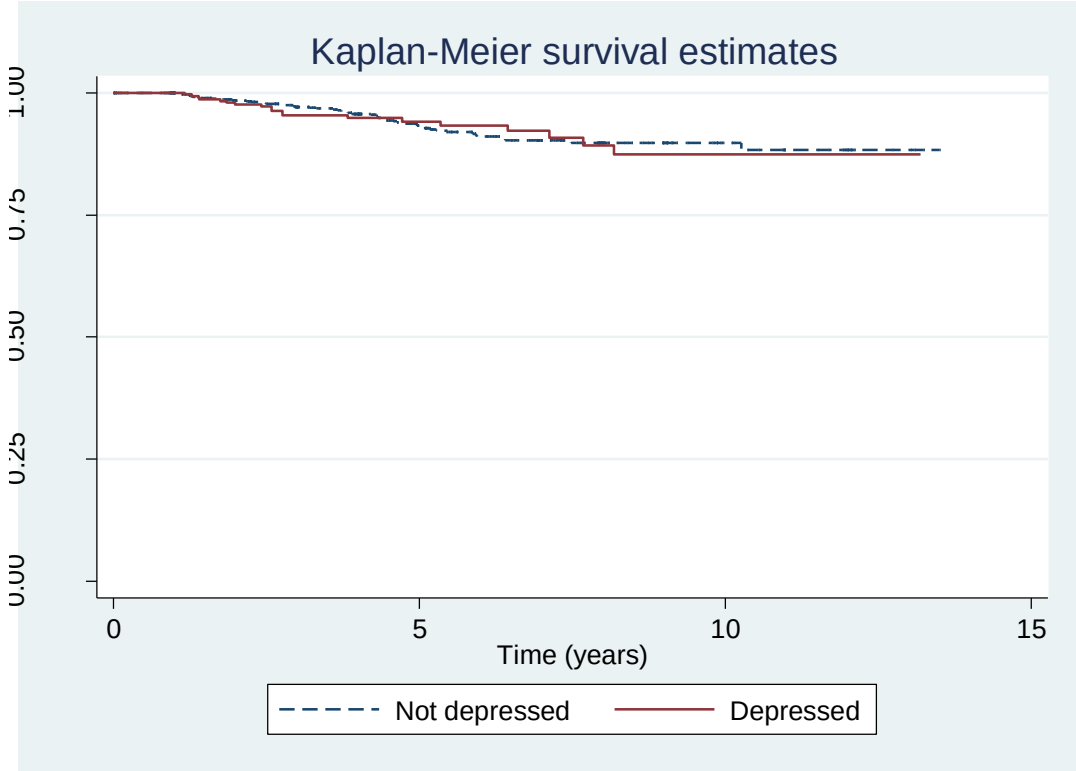
In the 15 years of follow-up stroke recurrences were recorded in 314 patients, and in another 205 patients, who were alive and recurrence free at three months and at one year respectively. Depression at three months, one year, or during year one, was not associated with higher risk

of recurrence at follow-up in univariate analysis. Figures 6.4, 6.5 and 6.6 show the Kaplan-Meier curves, and the log rank test results, for these associations.



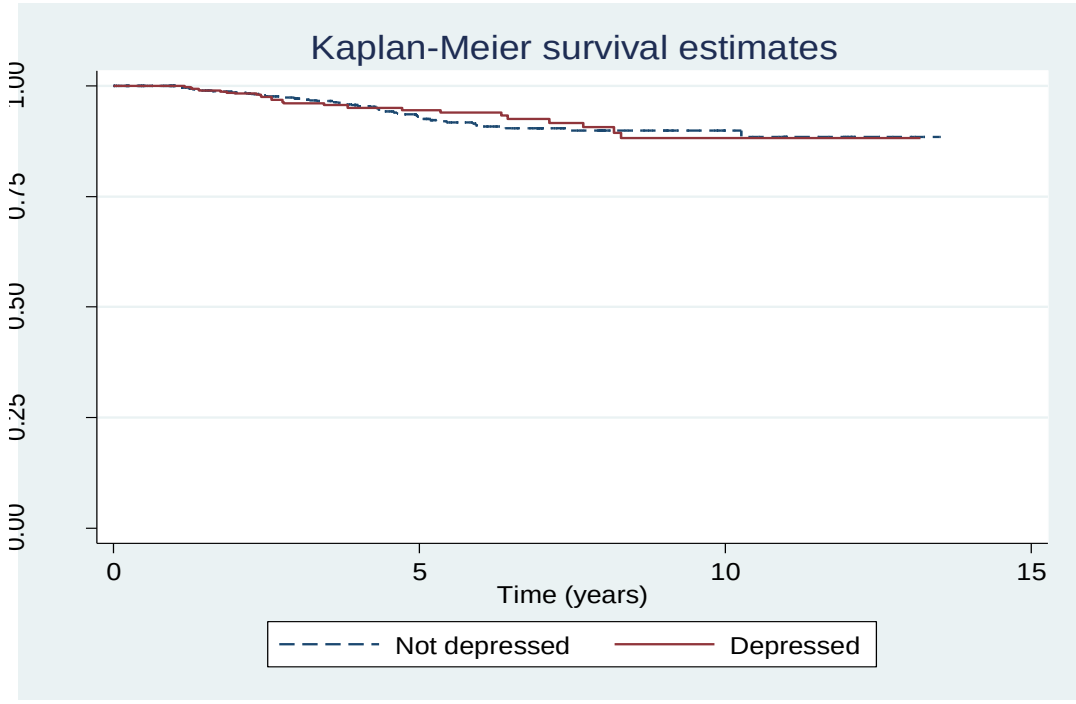
Log rank test p=0.7613

Figure 6.4 Recurrence rate by depression state at 3 months



Log rank test p=0.8458

Figure 6.5 Recurrence rate by depression state at 1 year



Log rank test p=0.8274

Figure 6.6 Recurrence rate by depression during year 1

The multivariate analysis did not show any significant difference in the risk of recurrence between patients with and without depression at three months, one year or during year one. (Table 6.4 and table 6.5)

	Hazard ratio	CI	p
Depressed at 3 months	1.03	0.64-1.65	0.903
Depressed at 1 year	1.18	0.69-2.00	0.550
Depressed during year 1	0.97	0.60-1.55	0.893

Table 6.4 Recurrence at follow-up of patients depressed at different time points. Multivariate analysis. Category for missing data included

	Hazard ratio	CI	p
Depressed at 3 months	1.09	0.61-1.94	0.779
Depressed at 1 year	0.83	0.45-1.54	0.558
Depressed during year 1	0.73	0.41-1.28	0.268

Table 6.5 Recurrence at follow-up of patients depressed at different time points. Multivariate analysis. Category for missing data not included.

The Kaplan-Meier curves showed some difference in the time free of recurrence in the first few years after stroke. Therefore the analysis was repeated but the time was limited to three years after stroke and then to five years after stroke. The univariate and multivariate analysis showed no difference in the risk of recurrence for patients with and without depression at three months, one year or either of these two time points, when the analysis was limited to three and five years after stroke.

6.4.3 Depression and disability

The univariate analyses showed that depression at three months, one year, and during year one was consistently associated with disability in the first five years of follow-up. The associations between depression and disability after year five were still consistent until year seven. There were some associations after year seven although they were not consistent and no significant associations were found from year 13 onwards. The relative risk was

consistently higher for the association between depression and severe disability than for the association between depression and mild disability.

The multivariate analyses produced similar results, with depression in the first year after stroke consistently showing an independent association with disability in the first five years. The associations were still consistent until year seven and then some less consistent associations were identified until year 12. The relative risk was also consistently higher for the association between depression and severe disability than for the association between depression and mild disability. (Tables 6.6 and 6.7)

	Disability	Depression at 3 months RR (95%CI)	Depression at 1 year RR (95%CI)	Depression during year 1 RR (95%CI)
1 year	Mild	2.80(1.93-4.07)**	2.05(1.49-2.82)**	2.45(1.85-3.26)**
	Severe	4.71(2.96-7.48)**	4.26(2.86-6.33)**	4.87(3.39-7.00)**
2 year	Mild	2.62(1.72-3.99)**	1.62(1.10(2.39)*	1.85(1.33-2.58)**
	Severe	3.61(2.08-6.26)**	2.53(1.52-4.21)**	2.75(1.77-4.27)**
3 year	Mild	1.96(1.24-3.09)**	2.34(1.52-3.60)**	2.00(1.39-2.87)**
	Severe	3.62(2.07-6.33)**	3.78(2.22-6.44)**	3.54(2.25-5.58)**
4 year	Mild	1.73(1.05-2.84)*	2.12(1.30-3.44)**	2.05(1.36-3.08)**
	Severe	3.28(1.74-6.17)**	3.38(1.82-6.27)**	3.61(2.14-6.09)**
5 year	Mild	1.51(0.83-2.75)	1.69(0.91-3.11)	2.03(1.22-3.38)**
	Severe	2.83(1.37-5.84)**	2.67(1.31-5.46)**	3.40(1.84-6.27)**
6 year	Mild	1.50(0.79-2.87)	2.52(1.34-4.72)**	1.73(1.03-2.92)*
	Severe	2.50(1.16-5.39)*	3.09(1.47-6.51)**	2.73(1.47-5.06)**
7 year	Mild	3.27(1.49-7.14)**	2.39(1.13-5.05)*	3.07(1.62-5.81)**
	Severe	3.14(1.12-8.80)*	2.92(1.21-7.01)*	2.91(1.34-6.35)**
8 year	Mild	1.57(0.64-3.88)	1.86(0.80-4.32)	1.92(0.93-3.94)
	Severe	1.47(0.53-4.03)	3.35(1.30-8.61)*	2.58(1.14-5.80)**
9 year	Mild	2.78(0.87-8.90)	3.28(1.13-9.51)*	2.83(1.18-6.81)*
	Severe	2.47(0.67-9.12)	5.53(1.73-17.67)**	2.84(1.05-7.66)*
10 year	Mild	1.57(0.35-7.06)	2.06(0.52-8.20)	1.60(0.52-4.93)
	Severe	1.62(0.31-8.46)	3.78(0.83-17.19)	1.66(0.48-5.78)
11 year	Mild	1.67(0.25-11.07)	1.30(0.33-4.78)	1.36(0.40-4.63)
	Severe	2.29(0.33-15.61)	5.06(1.12-22.80)*	4.05(1.01-16.20)*
12 year	Mild	1.30(0.09-17.91)	1.63(0.14-19.11)	2.58(0.35-18.93)
	Severe	5.11(0.29-88.38)	7.54(0.82-69.40)	8.61(1.07-69.17)*
13 year	Mild	-	2.35(0.09-57.23)	2.35(0.10-57.23)
	Severe	-	3.51(0.10-120.77)	3.52(0.10-120.77)
14 year	Mild	-.	-	-
	Severe	-	-	-
15 year	Mild	-	-	-
	Severe	-	-	-

Table 6.6 Disability at follow-up in patients with depression at different time points. Multivariate analysis. Missing data category included.

*** p<0.05**

****p<0.01**

	Disability	Depression at 3 months RR (95%CI)	Depression at 1 year RR (95%CI)	Depression during year 1 RR (95%CI)
1 year	Mild	2.75(1.75-4.30)**	2.42(1.67)**	2.58(1.84-3.61)**
	Severe	4.12(2.33-7.31)**	4.07(2.53-6.54)**	4.27(2.75-6.61)**
2 year	Mild	3.00(1.84-4.87)**	1.89(1.20-2.97)**	2.10*(1.42-3.10)**
	Severe	3.29(1.72-6.29)**	2.18(1.20-3.95)**	2.19(1.31-3.67)**
3 year	Mild	2.05(1.23-3.40)**	2.32(1.45-3.71)**	2.13(1.42-3.18)**
	Severe	3.28(1.74-6.18)**	3.78(2.11-6.75)**	3.27(1.97-5.41)**
4 year	Mild	1.75(1.00-3.07)*	2.05(1.21-3.47)**	1.95(1.25-3.06)**
	Severe	3.23(1.55-6.72)**	2.93(1.50-5.72)**	3.10(1.72-5.56)**
5 year	Mild	1.16(0.58-2.29)	1.26(0.64-2.49)	1.64(0.93-2.91)
	Severe	2.61(1.13-6.03)*	2.49(1.13-5.46)*	3.06(1.54-6.07)**
6 year	Mild	1.03(0.50-2.12)	1.99(1.02-3.89)*	1.40(0.79-2.47)
	Severe	1.68(0.67-4.22)	2.89(1.27-6.57)*	2.16(1.06-4,43)*
7 year	Mild	3.04(1.25-7.42)*	2.05(0.89-4.74)	2.66(1.30-5.47)**
	Severe	1.56(0.36-6.68)	2.44(0.88-6.78)	2.19(0.86-5.58)
8 year	Mild	3.23(0.98-10.63)	1.67(0.66-4.23)	2.42(1.06-5.53)*
	Severe	1.76(0.45-6.97)	3.25(1.11-9.48)*	3.06(1.11-8.42)*
9 year	Mild	5.53(0.83-36.63)	2.91(0.82-10.30)	2.81(0.99-7.94)
	Severe	5.81(1.01-33.49)*	4.31(1.16-15.93)*	2.51(0.83-7.60)
10 year	Mild	0.09(0.002-3.46)	20.58(1.22-346-67)*	2.54(0.53-12.27)
	Severe	0.14(0.002-9.45)	78.17(2.89-2112-77)*	2.75(0.39-19.28)
11 year	Mild	-	-	2.22(0.38-13.00)
	Severe	-	-	13.11(1.26-136.21)*
12 year	Mild	-	-	-
	Severe	-	-	-
13 year	Mild	-	-	-
	Severe	-	-	-
14 year	Mild	-	-	-
	Severe	-	-	-
15 year	Mild	-	-	-
	Severe	-	-	-

Table 6.7 Disability at follow-up in patients with depression at different time points. Multivariate analysis. No Missing data category included

*** p<0.05**

****p<0.01**

6.4.4 Depression and Cognitive Impairment

The univariate analysis showed that depression three months after stroke was associated with cognitive impairment in the first five years after stroke only in years one and two. After year five a significant association in year six was identified. Depression in year one was consistently associated with cognitive impairment in years one to five. After year five the associations were still consistent until year eight. Depression at either three months or one year was consistently associated with cognitive impairment in the first five years of follow-up. After that the associations were also significant in year six and in year eight

The multivariate analysis showed that depression after stroke was independently associated with cognitive impairment up until year eight. However, these associations were not entirely consistent for all the depression measurements and the cognitive impairment at all time points. (Table 6.8)

When the sensitivity analysis was conducted and the category for missing data was not included, depression at three months was not associated with cognitive impairment in any of the follow-up time points. Depression in year one, or at either three months or one year, were independently associated with cognitive impairment in years one to three, six and eight (Table 6.9)

Cognitive impairment	Depression at 3 months OR (95%CI)	Depression at 1 year OR (95%CI)	Depression during year 1 OR (95%CI)
1 year	1.66(1.11-2.47)*	1.84(1.30-2.62)**	1.53(1.12-2.09)**
2 year	1.49(0.96-2.30)	1.97(1.29-3.01)**	1.77(1.23-2.55)**
3 year	1.22(0.75-1.98)	2.01(1.28-3.14)**	1.49(1.01-2.19)*
4 year	1.05(0.61-1.80)	1.67(1.01-2.77)*	1.29(0.84-1.99)
5 year	1.51(0.79-2.86)	2.20(1.20-4.05)*	1.75(1.05-2.92)*
6 year	2.36(1.09-5.13)*	2.25(1.15-4.38)*	2.21(1.23-3.96)**
7 year	1.63(0.65-4.08)	2.40(1.07-5.43)*	2.11(1.03-4.30)*
8 year	1.48(0.49-4.43)	2.81(1.06-7.44)*	2.56(1.11-5.92)*
9 year	1.19(0.23-6.01)	1.79(0.44-7.29)	1.78(0.52-6.13)
10 year	--	0.42(0.04-4.37)	0.24(0.02-2.37)
11 year	2.78(0.18-42.02)	2.00(0.33-12.17)	2.11(0.36-12.44)
12 year	4.50(0.16-125.02)	0.83(0.03-23.18)	1.00(0.06-15.69)
13 year	-	-	-
14 year	-	-	-
15 year	-	-	-

Table 6.8 Cognitive impairment at follow-up in patients with depression at different time points with missing data category included

*** p<0.05**

****p<0.01**

Cognitive impairment	Depression at 3 months OR (95%CI)	Depression at 1 year OR (95%CI)	Depression during year 1 OR (95%CI)
1 year	1.61(1.00-2.60)	1.89(1.29-2.78)**	1.54(1.07-2.21)*
2 year	1.31(0.79-2.16)	2.00(1.24-3.21)**	1.89(1.24-2.90)**
3 year	1.51(0.86-2.65)	2.15(1.33-3.47)**	1.84(1.20-2.84)**
4 year	0.75(0.40-1.40)	1.66(0.95-2.88)	1.23(0.75-2.00)
5 year	1.09(0.49-2.44)	1.70(0.87-3.32)	1.20(0.66-2.16)
6 year	1.61(0.61-4.22)	3.30(1.51-7.19)**	2.81(1.41-5.63)**
7 year	1.44(0.39-5.25)	2.34(0.89-6.18)	1.95(0.84-4.53)
8 year	2.29(0.37-14.34)	4.56(1.30-15.95)*	3.76(1.20-11.83)*
9 year	-	-	-
10 year	-	3.60(0.10-129.36)	2.48(0.07-91.29)
11 year	-	-	18.37(0.52-646.98)
12 year	-	-	1.24(0.02-95.23)
13 year	-	-	-
14 year	-	-	-
15 year	-	-	-

Table 6.9 Cognitive impairment at follow-up in patients with depression at different time points with missing data category not included.

*** p<0.05**

****p<0.01**

6.4.5 Depression and mental domain of Health related quality of life (QoL)

Univariate analyses showed that depression after stroke was consistently associated with lower scores in the mental domain of QoL in the first eleven years of follow-up. Multivariate analyses showed that depression three months after stroke was associated with lower scores in the mental domain of QoL in years the first five years of follow-up. After that, the associations were still consistent until year seven and then in year eleven. Depression at year one, and at either three months or one year, was associated with lower scores in the mental domain of QoL in years one to nine. Depression at either three months or one year also predicted lower scores of the mental domain of QoL in year eleven. (Table 6.10) When the missing data category was not included in the analyses the results remained similar except for depression at three months that predicted lower scores also in year nine and depression at one year that predicted lower scores also in year eleven. (Table 6.11)

Quality of life (Mental domain)	Depression at 3 months OR (95%CI)	Depression at 1 year OR (95%CI)	Depression during year 1 OR (95%CI)
1 year	-8.19(-10.23- -6.15)**	-13.63(-15.17- -12.08)**	-11.53(-12.97- -10.08)**
2 year	-6.52(-8.42- -4.62)**	-7.76(-9.56- -5.97)**	-7.03(-8.57- -5.50)**
3 year	-6.34(-8.53- -4.15)**	-7.06(-9.18- -4.94)**	-6.84(-8.61- -5.07)**
4 year	-6.90(-9.08- -4.72)**	-6.42(-8.58- -4.26)**	-6.23(-8.04- -4.42)**
5 year	-6.24(-8.93- -3.55)**	-5.11(-7.79- -2.43)**	-6.21(-8.42- -4.00)**
6 year	-3.85(-6.88- -0.81)*	-7.41(-10.24- -4.59)**	-5.86(-8.27- -3.44)**
7 year	-4.98(-8.61- -1.35)**	-6.58(-10.24- -3.45)**	-6.78(-9.65- -3.91)**
8 year	-2.83(-7.08- 1.41)	-5.73(-9.66- -1.79)**	-3.95(-7.32- -0.58)*
9 year	-4.44(-9.97-0.69)	-8.18(-12.91- -3.44)**	-6.78(-10.78- -2.77)**
10 year	-2.22(-8.76-4.31)	-2.06(-8.05-3.93)	-2.48(-7.56-2.60)
11 year	-10.27(-17.64- -2.91)**	-5.76(-11.66-0.14)	-7.97(-13.47- -2.47)**
12 year	-0.71(-10.69-9.27)	0.96(-7.61-9.53)	-2.01(-9.98-5.97)
13 year	-	-5.25(-19.33-8.83)	-5.25(-19.33-8.83)
14 year	-	-	-
15 year	-	-	-

Table 6.10 Mental domain of quality of life at follow-up in patients with depression at different time points. Missing data category included.

*** p<0.05**

****p<0.01**

Quality of life (Mental domain)	Depression at 3 months OR (95%CI)	Depression at 1 year OR (95%CI)	Depression during year 1 OR (95%CI)
1 year	-9.05(-11.38- -6.72)**	-14.85(-16.53- -13.17)**	-12.40(-14.05- -10.74)**
2 year	-7.80(-9.96- -5.63)**	-7.96(-9.99- -5.94)**	-7.94(-9.72- -6.17)**
3 year	-6.67(-91.13- -4.22)**	-7.83(-10.11- -5.56)**	-7.47(-9.43- -5.51)**
4 year	-7.47(-9.96- -4.98)**	-6.40(-8.71- -4.09)**	-6.21(-8.26- -4.16)**
5 year	-6.26(-9.24- -3.28)**	-5.94 (-8.79- -3.08)**	-6.70(-9.12- -4.28)**
6 year	-4.14(-7.79- -0.50)*	-7.90(-11.29- -4.51)**	-6.79(-9.74- -3.83)**
7 year	-5.29(-9.54- -1.05)*	-7.52(-11.21- -3.83)**	-6.71(-10.00- -3.42)**
8 year	-3.10(-7.81-1.61)	-5.88(-10.03- -1.70)**	-4.79(-8.58- -1.01)*
9 year	-7.76(-14.96- -0.56)*	-10.19(-15.66- -4.73)**	-8.19(-12.65- -3.72)**
10 year	-6.08(-17.86-5.69)	-5.51(-13.35-2.07)	-3.64(-10.80-3.53)
11 year	-13.03(-20.41- -5.65)**	-8.47(-14.88- -2.07)*	-9.91(-15.65- -4.17)**
12 year	2.18(-10.50-14.87)	-2.94(-12.23-6.35)	-2.39(-10.545.75)
13 year	-	-5.34(-29.30-18.62)	-5.34(-29.30-18.62)
14 year	-	-	-
15 year	-	-	-

Table 6.11 Mental domain of quality of life at follow-up in patients with depression at different time points. Missing data category not included.

*** p<0.05**

****p<0.01**

6.4.6 Depression and physical domain of Health related quality of life (QoL)

Univariate analysis showed that depression after stroke was consistently associated with lower scores in the physical domain of QoL up to year 13. Multivariate analysis showed that depression at three months predicted lower scores of the physical domain of QoL in years one to seven. Depression at one year predicted lower scores in years one to eight. Finally depression at either three months or one year predicted lower scores in years one to nine and eleven to thirteen. (Table 6.12). When the missing data category was not included in the analyses the results were similar except for depression at one year that predicted lower scores also in year thirteen and depression at either three months or one year that no longer predicted lower scores in year eleven. (Table 6.13)

Quality of life (Physical domain)	Depression at 3 months OR (95%CI)	Depression at 1 year OR (95%CI)	Depression during year 1 OR (95%CI)
1 year	-4.53(-6.41- -2.65)**	-5.06(-6.59- -3.53)**	-5.60(-6.99- -4.20)**
2 year	-5.33(-7.21- -3.45)**	-3.95(-5.77- -2.14)**	-4.73(-6.27- -3.20)**
3 year	-6.03(-8.19- -3.87)**	-4.90(-7.03- -2.78)**	-5.85(-7.61- -4.09)**
4 year	-4.67(-6.84- -2.50)**	-5.22(-7.37- -3.06)**	-5.67(-7.46- -3.88)**
5 year	-5.14(-7.91- -2.38)**	-5.34(-8.08- -2.60)**	-5.96(-8.22- -3.69)**
6 year	-4.06(-7.11- -1.02)**	-5.47(-8.35- -2.60)**	-5.36(-7.80- -2.92)**
7 year	-5.61(-9.15- -2.08)**	-6.96(-10.47- -2.91)**	-7.00(-9.78- -4.22)**
8 year	-2.39(-6.51-1.72)	-6.69(-10.47- -2.91)**	-5.66(-8.90- -2.42)**
9 year	-4.07(-9.29-1.13)	-6.18(-10.38-0.70)	-5.64(-9.53- -1.74)**
10 year	0.61(-5.49-6.70)	-5.09(-10.65-0.47)	-3.31(-8.03-1.40)
11 year	-5.54(-12.65-1.57)	-6.31(-14.60-1.99)	-5.35(-10.60- -0.09)*
12 year	-6.53(-16.22-3.15)	-15.16(-26.73- -3.60)	-9.38(16.95- -1.81)**
13 year	-	-	-15.16(-26.73- -3.60)*
14 year	-	-	-
15 year	-	-	-

Table 6.12 Physical domain of quality of life at follow-up in patients with depression at different time points. Missing data category included.

*** p<0.05**

****p<0.01**

Quality of life (Mental domain)	Depression at 3 months OR (95%CI)	Depression at 1 year OR (95%CI)	Depression during year 1 OR (95%CI)
1 year	-4.59(-6.78- -2.40)**	-6.24(-7.96- -4.53)**	-6.37(-7.96- -4.78)**
2 year	-5.24(-7.37- -3.10)**	-4.63(-6.66- -2.61)**	-4.71(-6.47- -2.96)**
3 year	-5.76(-8.20- -3.33)**	-4.55(-6.80- -2.30)**	-5.11(-7.03- -3.19)**
4 year	-4.33(-6.78—1.87)**	-5.24(-7.58- -2.89)**	-5.38(-7.40- -3.36)**
5 year	-4.76(-7.86- -1.66)**	-4.86(-7.75- -1.97)**	-5.63(-8.11- -3.14)**
6 year	-4.24(-7.70- -0.78)*	-4.98(-8.06- -1.90)**	-5.36(-8.06- -2.66)**
7 year	-7.43(-11.86- -3.00)**	-7.32(-11.31- -3.32)**	-7.92(-11.38- -4.46)**
8 year	-2.28(-7.15- 2.58)	-6.60(-10.63- -2.57)**	-5.04(-8.68- -1.39)**
9 year	-2.95(-9.78- 3.87)	-8.78(-14.05- -3.50)**	-6.97(-11.35- -2.59)**
10 year	-3.45(-17.04-10.13)	-4.55(-12.38-3.27)	-3.34(-10.37-3.69)
11 year	-5.10(-15.22-5.03)	-6.28(-14.00-1.43)	-5.92(-12.88-1.05)
12 year	-4.41(-16.80-7.98)	-9.02(-18.33-0.29)	10.26(-18.03- -2.48)*
13 year	-	-29.38(-50.62- -8.13)*	-29.38(-50.62- -8.13)*
14 year	-	-	-
15 year	-	-	-

Table 6.13 Physical domain of quality of life at follow-up in patients with depression at different time points. Missing data category not included.

*** p<0.05**

****p<0.01**

6.5 DISCUSSION

Depression in the first year was independently associated with higher mortality, disability, cognitive impairment and lower quality of life up to 15 years after stroke. The consistency of these associations was different for each outcome. However, depression was not associated with stroke recurrence.

A previous systematic review[63] reported many possible health outcomes associated with depression after stroke, including higher disability rates, higher mortality, poor involvement in rehabilitation, longer hospital stay and poor cognitive function up to ten years after the acute event. However in that review, they included studies were depression and its potential outcomes had been assessed at the same time. This makes it difficult to know whether depression is actually cause or consequence of the variable investigated as potential outcome.

6.5.1 Depression and mortality

The association between depression and higher mortality after stroke had been reported before in two prospective studies of shorter follow-up and smaller sample size.[177] [178] Although the results of previous studies were not consistent, as another study found no association with high mortality at follow-up.[117] The SLSR data show a consistent rise of mortality associated with depression, independent of stroke severity, in the long term. This association maybe explained by the risk factors that depression and other life threatening diseases have in common, such as low level of exercise. Two systematic reviews reported the increased cardiovascular risk in patients with depression.[289] [290] A bio-behavioural model to explain the association between depression and cardiovascular diseases (CVD) has been proposed.[46] [47] This model includes variables varying from an increased presence of classical risk factors for CVD (such as smoking, hypertension and diabetes) to changes in the immune system and dysregulation of the autonomic nervous system.

6.5.2 Depression and stroke recurrence

No association was found between depression after stroke and stroke recurrence. Considering that a stroke recurrence is a cardiovascular event, the results presented in this chapter are not consistent with the ones reported in two systematic reviews that showed an increased cardiovascular risk amongst patients with depression.[289] [290] It seems that after a first stroke, depression is a less relevant cardiovascular risk factor than before stroke. The results presented in this chapter confirm the results previously obtained with a smaller SLSR dataset and different analysis.[291] The predictors of stroke recurrence identified in that study were atrial fibrillation, previous myocardial infarction, hypertension and old age, which are classical risk factors for stroke. The same bio-behavioural model that may explain the association between depression and cardiovascular risk[46] [47] doesn't seem to be valid for the association between depression and stroke recurrence.

Since the methods used to register first ever strokes and recurrent ones were similar, and strokes are well recorded as major events in medical notes, it was considered unlikely that a large number of recurrent strokes had been missed. Therefore, it was judged that missed recurrences did not have a relevant effect on these results.

6.5.3 Depression and disability

The association between depression after stroke and disability at follow-up had been reported before in a hospital study where 293 patients were assessed for depression during the acute phase of stroke and a year later they were assessed for disability. The OR for disability in depressed patients was 2.51 (1.35-4.68).[179] The ORs presented in this chapter range from 1.75 to 4.14. It was also observed in this chapter how the risk of having severe disability is more increased than the risk of having mild disability for patients who have depression shortly after stroke. The ceiling effect of the BI, which gives patients with various degrees of disability the

minimum score, may partly explain the difference on the strength of these associations. While this limitation was acknowledged, the good metric properties of the BI,[198 199] should be noted as well. The association between depression and disability at follow-up may be explained by the poor involvement in rehabilitation that has been observed in the six weeks following a stroke[63] or simply by the low level of activity they have, that was reported in the previous chapter of this thesis.

6.5.4 Depression and cognitive impairment

The association between depression and cognitive impairment remains complex, as both can be cause and effect of each other. A systematic review of cognitive impairment in depressed patients from the general population reported a significant correlation between decreased cognitive performance and increased depression severity.[296] Nonetheless, studies were cognition and depression had been assessed at the same time point were included in that review. Without the temporal sequence is difficult to attribute causality of one to the other. Cognitive impairment can be a consequence of stroke as well.[259] However, since our analysis was adjusted for stroke severity measures, and depression was observed at earlier time point than cognitive impairment, we can infer some degree of causation in the association between depression shortly after stroke and impaired cognition at follow-up.

The limitations of the MMSE and the AMT have been discussed in chapter three. The association between depression and cognitive impairment may be weaker than the estimated in patients with low level of education as they tend to score lower in the cognition tests.[209] It should be noted that both scales have been validated against the clinical assessment of patients, showing both of them very good psychometric properties.[209 210]

6.5.5 Depression and Quality of life

The association between depression and lower quality of life in the first year after stroke has been reported before.[179] [180] This chapter shows the very consistent association between depression and lower quality of life, both the mental and physical domains, in the very long term. Since depression affects the physical, psychological and social domains[31], of patient's life, the association between depression and lower quality of life was expected. The possible overlapping between the HAD scale and the QoL measure may explain in part these results. This may be the case particularly for the associations between the depression and the mental health domain of QOL.

6.5.6 Strengths and limitations

This chapter has strengths and limitations. Using a population based register with repeated assessments of a large number of patients in the long term, allows to obtained results less biased than in hospital or rehabilitation studies. It also allows conducting robust statistical analyses with high statistical power able to identify minor differences between patients that may not have been observed in studies of smaller sample size. The description of the impact of depression in the long term is another strength of this chapter. However the analyses could only be conducted in patients with available data for depression. It is possible that the proportion of depressed patients amongst those who are lost to follow-up is higher than in those who are followed up. Some of the outcomes investigated, such as cognitive impairment and disability are strongly associated with depression. Therefore our analysis may still be underestimating the risk of cognitive impairment and disability in patients with depression. Since missing data on depression was over 30% in most cases it was decided not to use multiple imputation as it would have introduced error.[234] [263] Sensitivity analysis was then the method chosen to deal with missing data on depression. Estimates obtained when the

category for missing data was included were consistent with the ones obtained when it was not in the analyses. To report this consistency the tables show estimates using both the category for missing data and not using it. One possible explanation for this result is that patients who have missing data are not very different from those with complete data. One factor in favour of some similarity between patients lost to follow-up and those who were followed up is that depression data was not routinely collected from any patients in the first two years of the register. Missing data for these patients is missing completely at random for this period of time therefore not introducing bias.

The estimation of clinical outcomes using scales introduces some limitations although all scales have good performance and they allowed assessing a very large number of patients during a long follow-up, which would not have been possible otherwise.

As discussed before these results may be affected by residual and unmeasured confounding. The election of confounders, the form in which confounders should enter the model, or the time scale over which they act are uncertain. In this thesis the variables included in the models were informed by the systematic review presented in chapter two. The potential source of bias due to unmeasured confounding has been minimised using methods of dealing with missing data. [280]

6.5.8 Implications for clinical practice

Depression after stroke deserves clinical attention as it is not only a distressing outcome of stroke but an independent predictor of higher mortality, disability, cognitive impairment and lower quality of life in the long term. Considering the difficulty that clinicians have to screen stroke patients for depression[53] it is important that patients report their symptoms. Therefore, patients and carers should be made aware of the relevance of depression. The active role that

patients are supposed to have in clinical management of their problems[250] would help in the prompt clinical approach to depression after stroke.

Some patients, such as those with cognitive impairment, are particularly difficult to assess for depression. Clinicians should know that depression may be a treatable cause of the cognitive impairment observed in some stroke patients.

6.5.8 Implications for future research

The results of this chapter raise some questions that could be approached in further research.

There is a wide variety of potential mechanisms underlying the possibly elevated risk of cardiovascular disease in depressed patients. Further studies are needed to understand the impact of these mechanisms.

A randomised controlled trial recently presented a significantly better functional outcome three months after stroke in patients treated with fluoxetine and physiotherapy than in those receiving physiotherapy only.[310] Further clinical trials could aim to confirm these results and also to investigate whether intervening on depression after stroke results in a reduction of mortality, and cognitive impairment in the long term and an improvement in quality of life. If effective interventions on depression after stroke actually improve the long term prognosis of stroke, a substantial change in clinical practice could be suggested.

CHAPTER 7 CONCLUSIONS FROM THIS THESIS

As discussed in chapter one stroke and depression are both important causes of loss of DALYs globally. Depression is highly prevalent among patients with long term conditions and it may be associated with poor health.

The results of this thesis show that depression has a dynamic natural history, it affects more than one in two patients at some point, with a persistent prevalence around 30%, up to 15 years after stroke. The risk of depression is higher amongst those with previous depression, severe strokes, and social isolation. Finally depression is independently associated with negative health outcomes in the long term. While these results may have limitations, they show that the hypothesis raised initially has been tested, providing evidence applicable in clinical practice, public health and further research.

7.1 SUMMARY OF FINDINGS OF THIS THESIS

The systematic review presented in chapter two identified 49 studies, published between 1983 and 2011, estimating the natural history, predictors, or associated health outcomes of depression after stroke. Most studies had limitations including selection bias, with only six population based studies, small sample size, short follow-up, and weak analysis.

The pooled prevalence of depression after stroke was around 29%. The incidence, reported only in one study, was 10% one year after stroke. The cumulative incidence rates in the first year after stroke, reported in two studies, were 39 and 48%. Evidence was poor, or lacking, on the long term natural history of depression after stroke, including its prevalence, incidence, cumulative incidence, time of onset, duration and recurrence.

Nine studies also reported variables present at baseline or at follow-up associated with depression after stroke. However, the limitations of these studies make their results difficult

to apply in clinical practice. The identification of stroke patients at highest risk of depression in the long term, on which interventions should focus, is still unclear.

Five studies of unselected stroke patients have investigated the association between depression and other negative health outcomes in the long term including mortality, lower quality of life and disability. However, most of them did not report their methods adequately and therefore their results are difficult to interpret. The associations between depression and other relevant health outcomes, such as stroke recurrence and cognitive impairment, have not been investigated. To understand the impact of depression after stroke it is necessary to investigate the possible association between depression and mortality, stroke recurrence, disability, cognitive impairment, and quality of life in the long term.

A population based cohort study of stroke patients, with large sample size, broad range of sociodemographic and clinical variables, collected at baseline and at follow-up, for over ten years, provides an ideal dataset to investigate depression after stroke in the areas where evidence is still insufficient. The South London Stroke Register, as a prospective longitudinal population based stroke register, established in a multi-ethnic, inner city population of 271,817, meets all these criteria. The analysis of data collected by the South London Stroke Register between 1995 and 2009 allows estimating the natural history, predictors and associated health outcomes of depression up to 15 years after stroke. Some of the limitations of this dataset, such as the missing data, can be addressed with statistical methods, including inverse probability weighting, multiple imputation and sensitivity analysis.

The results of the analyses of the SLSR data presented in this thesis showed that the prevalence of depression was around 30% and remained stable in the 15 years following a stroke, with incidence ranging from 7 to 21% and cumulative incidence of 55%. Most episodes of depression started shortly after stroke, with 33% of them starting in the three

months following a stroke, and no new episodes were identified from year ten onwards. 50% of the patients with depression at three months had recovered one year after stroke. The majority of the patients developing depression in the long term had had episodes of depression shortly after stroke suggesting that patients not becoming depressed shortly after stroke may not become depressed at all. Weighted estimates were consistent with the crude ones, therefore the validity of results from complete case analysis should be considered.

Stroke severity, disability seven days after stroke, depression before stroke, and depression and anxiety three months after stroke, were the baseline variables most consistently associated with depression up to 15 years after stroke. Disability, social isolation, low level of activity and cognitive impairment were the follow-up variables most consistently associated with depression at follow-up.

There were a small number of variables predicting outcomes of the natural history of depression after stroke. The risk of depression at some point after stroke can be predicted with sociodemographic and clinical observations. However, the association of these variables with other measures of the natural history of depression, including time of onset and duration of depression, is much weaker.

Depression in the first year after stroke was associated with higher mortality up to 15 years after stroke. No significant association was identified between depression and stroke recurrence. Disability and cognitive impairment rates were also significantly higher amongst patients depressed in the first year after stroke. Depression after stroke also showed a consistent association with lower quality of life in the 15 years following a stroke.

7.2 IMPLICATIONS FOR CLINICAL PRACTICE

These results suggest that clinicians have to acknowledge that depression is a very common outcome after stroke, which may affect patients in the very long term. Health care professionals with the primary responsibility for patient care may be best situated to identify stroke patients who may have depression.[311]

Since the time of highest risk for depression is shortly after the acute event, the best moment for the first screening may be during the acute phase. However, while screening for depression seems logical in stroke patients there is no evidence to show that screening alone improves management or treatment of depression in non mental health settings.[312] The evidence suggests that screening only improves depression management when there is a clear treatment strategy that is monitored and has clear stopping rules.[53] General practitioners use various methods to assess mental health risk, which include observing patient presentation, asking direct questions, decision support software and using risk assessment scales for detecting the risks of suicide, anxiety and depression. The main tool used in the UK is the Patient Health Questionnaire 9, but other risk-specific tools, such as the Hospital Anxiety and Depression Scale and the Generalised Anxiety Disorder (GAD-7) are also used.[313] This diversified approach gives clinicians some flexibility, however not screening for depression in a systematic way means that some important pieces information may be missed. The assessment of depression in patients with physical conditions, stroke in particular, maybe more complex than in general population. This may be because of the uncertain boundaries among clinical and non pathological psychological symptoms and the overlap between symptoms of depression and physical disorder. Some of the risk assessments tools, such as the Hospital Anxiety and Depression scale were designed to be used in patients with other medical problems and show a good performace in stroke patients. Having a more systematic

approach to the assessment of depression after stroke would ensure coverage of all the risk areas which need to be considered. Screening would become more effective if the results presented in this thesis were considered. Screening could start shortly after stroke and patients could continue to be assessed periodically in primary care. The nature of screening and its timing requires investigation. Patients who do not become depressed shortly after stroke seem to be at lower risk for depression. Except in these patients, depression requires periodic clinical attention in the long term. The high rate of recurrence of depression should be acknowledged. The assessment of patients at high risk of depression, at a moment of high risk, may improve the positive predictive value of the screening tools reducing the number of patients that receive unnecessary assessment after the first approach.

Primary care settings have an advantage over hospitals when considering long term interventions as follow-up examination may be routine, brief, and easy to arrange. In the UK, one of the elements driving primary care is the Quality of Outcomes Framework (QOF),[283] a scheme that rewards general practices for performance against clinical quality indicators. QOF has raised some controversy but it has also proven to improve quality of care in some areas including cardiovascular health.[314 315] Unlike in diabetes or coronary artery disease, the assessment for depression after stroke is not a quality indicator included in the QOF. This is likely to lead GPs not to assess stroke patients for depression in the long term. The results of this thesis show that depression has a high impact on stroke patients. Therefore, policy makers could consider including the assessment for depression among long term stroke survivors at high risk of depression in the QOF.

The Cochrane reviews on preventive and therapeutic interventions for depression after stroke showed a small but significant effect of psychotherapy on preventing depression and also a small but significant effect of pharmacotherapy on treating depression, as well as an increase

in adverse events.[78] [79] Targeted interventions in patients at an increased risk of depression, and delivered at the moment of highest incidence, are likely to be more effective. This applies to all kind of interventions, screening, diagnosis, prevention, treatment, follow-up and re-assessments in the long term. Therefore, especial attention should be given to patients who have recently had a stroke and also to patients with severe strokes, disability, depression before stroke, and depression and anxiety shortly after stroke. Clinicians should also be aware of the high risk of depression amongst patients with cognitive and communication impairment, who may be unable to report their symptoms. While patients with severe strokes are the most vulnerable and they constitute a group on which interventions should be developed, the strong association between depression and disability in the long term may make treatments for depression less effective in the most disabled patients.

Depression after stroke should be approached holistically. Treatment that is solely directed towards the symptoms of depression without strengthening coping skills may leave the patients with a persistent vulnerability to subsequent adaptive failure and depressive episodes.[20] Probably the biggest obstacle to routine use of psychological strategies is access to trained therapists due to scarcity of services, long waiting lists for non crises cases, and financial cost. However, the psychotherapeutic assitance may be provided not only through a formal process of psychoterapy, but also in the context of the ongoing doctor-patient relationship. For many people with medical conditions the relationship with a clinician who is prepared to listen to their experience is the most important component of their treatment.[20] Although the therapeutic relationship may be one of the most powerful tools to preserve and protect emotional well-being, this factor is often underestimated by practicing physicians. Appropriate training of clinicians to make the relationship with the patient psychotherapeutic on itself could be suggested. Some medical patients who might benefit from psychoterapy may be relucant to accept a treatment that implies that they are “damaged” in yet another

way. These patients may prefere brief and periodic interventions that emphasize psychoeducation.

Considering the difficulty that clinicians have to detect depression in stroke survivors[53] it is important that patients report their symptoms. Therefore, patients and carers should be made aware of the relevance of depression. The active role that patients are supposed to have in clinical management of their problems[250] would help in the prompt clinical approach to depression after stroke.

It has been suggested that health services may not have the resources to treat all the patients diagnosed with a more effective screening policy.[53] Nonetheless, depression is associated with negative health outcomes that would be costly for the health service in the long term. While further research into the benefit of psychological care after stroke is needed, there is already some evidence suggesting that an effective management of depression after stroke may be a cost effective policy.[316]

Many of the predictors of depression after stroke identified in this thesis are not specific of stroke. Previous history of depression or disability for example can be present in patients affected by other long term conditions. While depression has been approached several times in patients with common long term condition, such as diabetes or COPD,[22 57-59 81] it has received little attention in the context of other less common diseases. The findings of this thesis could raise the hypothesis that depression may also be a frequent and recurrent problem affecting patients with other less common chronic conditions in the long term and leading to poor health outcomes. This hypothesis could inform both management strategies and further research studies.

It has been reported that patients with multi-morbidity often receive care from different teams in an uncoordinated way.[80] The results of this thesis, together with studies of depression in

the context of other diseases,[22 57-59 81] suggest that depression may be relevant to patients affected by most long term conditions.[19] An integrated approach to depression, not only for diabetics and patients with coronary artery disease, but for all the chronically ill, including stroke survivors and also patients with less frequent problems, might be suggested. All patients with long term conditions could be assessed for depression periodically in the primary care clinic, which is where the medical management of different problems is integrated.

7.3 IMPLICATIONS FOR FUTURE RESEARCH

Future clinical trials of interventions for depression after stroke may also consider the evidence provided in this thesis. The moment of highest risk, in which interventions can be tested, is the first year after stroke. The effect of interventions should be observed shortly after being started, as most episodes of depression show short duration. Patients with severe strokes, disability, social isolation, and anxiety in the acute phase are the ones in which future clinical trials should focus. Patients not depressed shortly after stroke are less likely to become depressed in the long term and therefore interventions on them are less likely to show a significant effect. However, patients who have depression shortly after stroke are at high risk of having a recurrent episode and interventions in the long term may also be needed. Future clinical trials could aim to investigate whether intervening on depression after stroke results in a reduction of mortality, cognitive impairment in the long term, or an improvement in quality of life.

In studies of burden and outcomes of disease the years of life lived with disability (YLDs) are computed as the prevalence of different disease sequelae multiplied by the disability weight for that sequel. These studies use published estimates of prevalence, incidence, remission, and excess mortality of each sequel as source of data.[5] Therefore the results on the long term

natural history and outcomes of depression after stroke presented in this thesis could inform studies of burden and outcome of stroke in the future. Similarly, studies of burden of disease and outcomes of depression, use estimates of natural history and mortality for their analyses.[2] [5] The results presented in this thesis could inform these studies in the future improving the estimation of loss of DALYs attributed to mental and behavioural disorders.

This thesis has reported that depression is a very frequent problem after stroke, representing the emotional burden of the disease, in the long term. Future interventions on stroke patients aiming to reduce the long term consequences of stroke may use depression as one of the measures of effect. Depression could also be used by health authorities to evaluate the quality of care provided to stroke patients both in the hospital and in the community. With the results of this thesis it could be hypothesized that a more effective management of stroke and better quality of care could lead to lower frequency of depression in the long term.

The categorisation of patients as depressed and not depressed is clinically useful but does not reflect the reality of patients' mood accurately as depressive symptoms are continuously distributed in populations. The severity of the depression after stroke, and its clinical relevance, remain a matter of further research. Tools specifically validated to assess degrees of severity of depression will be required in these studies.

Patients with communication and cognitive impairment deserve to be studied specifically. The results of this thesis show that the risk of depression may be particularly high in these patients. However, they are difficult to assess and they have been excluded from many studies of depression after stroke. The association between depression and cognitive impairment remains complex, as both can be cause and effect of each other. The development of effective interventions for depression after stroke would clarify what is the relevance of depression on the aetiology of cognitive impairment.

There is a wide variety of potential mechanisms underlying the elevated risk of cardiovascular disease, other diseases, and overall mortality, in depressed patients. Further etiological and psychobiological studies are needed to understand the nature of these mechanisms.

Observational studies on cohorts of patients with post-stroke depression should also identify predictors of negative health outcomes of depression that may inform future studies and interventions. For example, if lack of exercise and social isolation are found to be predictors of higher mortality amongst patients with post-stroke depression, interventions encouraging exercise and socialisation could be proposed for depression. Some of the potential predictors to be investigated may be measures that are already in place, such as attendance to day centres, district nurse care, or GPs' medication reviews.

The effect of antidepressants on depression and other outcomes of stroke deserves special attention as these drugs are already being prescribed to many stroke patients. The Cochrane review on pharmacological interventions to treat depression after stroke showed a limited effect of drugs on patients mood.[79] A recent Cochrane review investigating the effect of antidepressants on stroke recovery reported that Selective Serotonin Reuptake Inhibitors appeared to improve dependence, disability, neurological impairment, anxiety and depression after stroke, but there was heterogeneity between trials and methodological limitations in a substantial proportion of the studies reviewed. Furthermore this review could not find enough evidence on the potential harmful effects of antidepressants.[56] Another systematic review found a positive association between the use of antidepressants and stroke risk. The authors of this review interpreted their result cautiously considering that medication use could be a marker of depression severity, and many studies lacked information on dose and duration of medication use.[290] Observational studies may clarify the effect of antidepressants on patients' mood, functionality, and mortality after stroke. The clinical trials

currently running on antidepressants to improve stroke recovery,[317] and further trials testing other interventions, may be informed by these observational studies.

Most predictors of depression are not purely biological. In the development of future interventions a complex approach to depression, that does not include only drugs, should be considered. This may have to be delivered in cooperation with professionals working outside the health service. There is a need for trials establishing the efficacy of a broader range of treatment and prevention strategies including the provision of combined and collaborative care interventions, talking interventions delivered by trained and supervised lay workers, and trials of guided self help.

One of the findings of this thesis is that depression and anxiety are strongly associated amongst stroke patients. However, despite being the most common mental health disorder globally, anxiety after stroke has received comparatively less attention than depression.[318 319] Previous studies of anxiety after stroke have limitations including small sample size and short follow-up.[318] There is also scant information about the long term natural history and predictors of anxiety after stroke.[320] It is also poorly understood whether anxiety after stroke is associated with other health outcomes such as mortality, disability, stroke recurrence, cognitive impairment and lower quality of life in the long term. The evidence on the long term natural history, predictors and outcomes of anxiety after stroke, is still insufficient to inform prognosis and treatment strategies.[10 320] Further studies are needed that estimate the incidence, cumulative incidence, prevalence and time of onset of anxiety in the long term after stroke, its predictors, and its potential association with mortality, disability, stroke recurrence, cognitive impairment and quality of life in the long term.

In this thesis the association between stroke and depression has been discussed in depth. However, it has also been observed that a large proportion of stroke patients do not develop

depression. This is consistent with other previous epidemiological studies, showing that a significant proportion of patients with physical illness do not develop psychopathology, and introduces the concept of resilience.[20 321] Resilience has been defined in a psychiatric context as the ability to thrive in the face of the adversity,[321] to cope with stress,[322] or to bounce back after adversity.[323] Determinants of resilience have been found at different levels including genetic, biological, psychological, family, community, social, and environmental.[321-324] The study of resilience has become more relevant in recent years as there has been a shift from problem-orientated approach to one that stresses prevention and the nurturing of strengths.[324] Resilience has been investigated in people who had gone through many different stressful events and situations.[321] There are trials that have reported successful interventions enhancing resilience in diabetes,[325] post-traumatic stress,[326] academic stress,[327] multiple sclerosis,[328] and stress at work.[329] However, even though resilience is an interesting concept that opens a new way of looking at mental health problems in the medically ill, its routine application in clinical practice requires further research. A good conceptualization of resilience and its potential role in stroke patients is important as it may allow development of interventions to prevent and/or treat post stroke depression.

Clinicians, patients, and carers beliefs about depression after stroke also influence the effectiveness of its management. We need approaches to depression after stroke which are sensitive to these beliefs. Further qualitative research studies investigating what doctors, patients and carers think about depression after stroke, and its possible clinical approach, may also help in the development of effective interventions. Stroke survivors should be included in the planning and design of further research to ensure that the outcomes and methods are relevant to them. Finally, future studies describing the natural history, predictors and outcomes of depression after stroke, and the effect of interventions, in low-and middle-income countries are also required.

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APPENDICES

APPENDIX 1. PUBLICATIONS ARISING FROM THIS WORK

PAPERS

Ayerbe L, Ayis S, Rudd AG, Heuschmann PU, Wolfe CDA Natural history, predictors and associations of depression 5 years after stroke; the South London Stroke Register. Stroke Stroke. 2011;42(7):1907-11.

Addo J, Ayerbe L, Mohan K, Crichton S, Sheldenkar A, Chen R, Wolfe CDA, McKevitt C. Socioeconomic status and stroke- an updated review. Stroke. 2012;43(4):1186-91.

Ayerbe L, Ayis S, Wolfe CDA, Rudd AG. A systematic review and meta-analysis of depression after stroke, its natural history, predictors, and outcomes. Br J Psychiatry. 2013; 202(1):14-21

Ayerbe L, Ayis S, Crichton S, Wolfe CDA, Rudd AG. The natural history of depression up to 15 years after stroke; the South London Stroke Register. Stroke. 2013;44(4):1105-10.

Ayerbe L, Ayis S, Crichton S, Wolfe CDA, Rudd AG. The long term outcomes of depression up to ten years after stroke; The South London Stroke Register. J Neurol Neurosurg Psychiatry. 2013 Oct 25

PRESENTATIONS

Ayerbe L, Ayis, S, Rudd A, Wolfe CDA. Depression after stroke predicts health outcomes in the long term. European Stroke Conference Hamburg 24th-27th May 2011. Oral presentation.

Ayerbe L, Ayis, S, Rudd AG, Wolfe CDA. The natural history of depression up to 15 years after stroke. European stroke Conference. Hamburg 24th-27th May 2011. Oral presentation.

Ayerbe L, Ayis, S, Rudd AG, Wolfe CDA. Prevalence and predictors of depression after stroke; the South London Stroke Register. European Stroke Conference. Barcelona 25th-28th May 2010. Poster

APPENDIX 2. SLSR INITIAL FORM

Draft

SOUTH LONDON STROKE REGISTER

ID Number

INITIAL FORM V19

Interviewer ID

1. Date of interview

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year : 2011 2012 2013 2014 2015

NOTIFICATION DETAILS

2. Date of notification

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year : 2008 2009 2010 2011 2012 2013

3. Notification Sources

Please select ALL relevant answers

- 1. GP and practice staff
- 2. Ambulance doctors
- 3. Practice computer records
- 4. Hospital staff
- 5. Hospital computer records
- 6. Radiology records
- 7. Accident and Emergency
- 8. Community therapists
- 9. Post mortems
- 10. Coroner's records
- 11. Death certificates
- 12. Research teams/ward checks
- 13. Bereavement officer
- 14. Bed manager
- 15. Nursing home
- 16. Neurovascular clinic
- 17. Other *Specify:* _____

4. Primary source of notification:

SOCIODEMOGRAPHIC DETAILS

5. Date of Birth

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: 1800 1900 2000 0 1 2 3 4 5 6 7 8 9

6. Sex

Male Female

7a. Ethnic Group

Information to be obtained directly from patient.

White
- British
- Irish
- Other White background

Black or Black British
- Caribbean
- African
- Other Black background

Mixed
- White and Black Caribbean
- White and Black African
- Other mixed background
- White and Asian

Asian or British Asian
- Bangladeshi
- Indian
- Pakistani
- Other Asian background

Other ethnic categories
- Chinese
- Any other ethnic category

Not stated
- Not stated

7b. Was the patient born in the UK?

- Yes → Go to question 7d
- No
- Unknown → Go to question 7d

7c. Country of Birth of Patient

7d. Country of Birth of Patient's Father

7e. Country of Birth of Patient's Mother

8. Living Conditions Prior to Stroke

- Private household alone
- Private household with others
- Sheltered home
- Residential home
- Nursing home
- Community hospital
- Private hospital
- Long term hospital care
- Unknown
- Other *Specify:* _____

9a. In the last 2 weeks, has the patient required help from another person for everyday activities (such as making a cup of tea)?

- Yes
- No → Go to question 10
- Unknown → Go to question 10

9b. If yes, who did the patient receive most help from? (select one)

- Home help or carer
- Spouse/partner
- Daughter
- Other *Specify* _____
- Son
- Other relative
- Other professional care (paid/unpaid)
- Unknown
- Friend
- Voluntary Organisation

10. Patient's Education Level

Information to be obtained directly from patient.

- No formal education
- Primary
- Lower secondary
- Upper secondary
- Post secondary non tertiary
- First stage of tertiary
- Secondary stage of tertiary
- Unknown

11. Employment Status Prior to Stroke

- Full time employed *(more than 30hrs/wk)*
- Part time employed *(less than 30hrs/wk)*
- Retired
- Unknown
- Carer for home/family/dependents
- Unemployed and looking for work
- Unable to work due to disability/ill-health

12. Patient's Occupation (Please insert most recent occupation)

13. Employment status (in most recent occupation)

- ☐ Self-employed with 25 or more employees
- ☐ Self-employed with less than 25 employees
- ☐ Self-employed with no employees
- ☐ Manager in establishment with 25 or more employees
- ☐ Manager in establishment with less than 25 employees
- ☐ Supervisor
- ☐ Employee
- ☐ Unknown

RISK FACTORS PRIOR TO STROKE

14a. Is there a recent GP/hospital BP record prior to stroke?

- ☐ Yes
- ☐ No → Go to question 15
- ☐ Unknown → Go to question 15

14b. What was the recorded BP?

SBP ☐☐☐ DBP ☐☐☐

14c. What date was the BP recorded?

Day:	10 ☐	20 ☐	30 ☐	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	
Month:	Jan ☐	Feb ☐	Mar ☐	Apr ☐	May ☐	Jun ☐	Jul ☐	Aug ☐	Sept ☐	Oct ☐	Nov ☐	Dec ☐		
Year:	1990 ☐	2000 ☐	2010 ☐	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	

15. Is there a recent GP/hospital record ofany of the following diagnosis prior to stroke?

Hypertension	☐ Yes	☐ No	☐ Unknown
Congestive Cardiac Failure	☐ Yes	☐ No	☐ Unknown
Angina	☐ Yes	☐ No	☐ Unknown
Hypercholesterolaemia	☐ Yes	☐ No	☐ Unknown
Peripheral vascular disease	☐ Yes	☐ No	☐ Unknown
Oral Contraceptive pill (in last 6 months)	☐ Yes	☐ No	☐ Unknown
Sickle cell disease	☐ Yes	☐ No	☐ Unknown
Migraine	☐ Yes	☐ No	☐ Unknown
Atrial fibrilation	☐ Yes	☐ No	☐ Unknown
TIA	☐ Yes	☐ No	☐ Unknown
Depression	☐ Yes	☐ No	☐ Unknown

16a. Is there a recent GP/hospital record of Myocardial Infarction (MI) prior to stroke?

- ☐ Yes
- ☐ No → Go to question 17
- ☐ Unknown → Go to question 17

16b. How long ago was the MI?

- ☐ <1 month ago
- ☐ 1-6 months ago
- ☐ over 6 months ago

17a. Was the patient diabetic prior to stroke?

- ☐ Yes, on insulin
- ☐ Yes, on oral hypoglycaemics
- ☐ Yes, diet control only
- ☐ Yes, on insulin and oral hypoglycaemics
- ☐ No → Go to question 18
- ☐ Unknown → Go to question 18

17b. Is the last HbA1c prior to stroke known?

- ☐ Yes
- ☐ No → Go to question 18
- ☐ Unknown → Go to question 18

17c. What was the last HbA1c? ☐☐.☐

18a. Is there a family history of vascular diseases, such as stroke or MI, in the patient's biological family (i.e. biological father, biological mother or siblings)?

- ☐ Yes
- ☐ No → Go to question 19
- ☐ Unknown → Go to question 19

18b. If yes:

	Stroke	Age at first stroke	MI	Age at first MI
Father	☐ No ☐ Yes ☐ Unknown	☐☐☐	☐ No ☐ Yes ☐ Unknown	☐☐☐
Mother	☐ No ☐ Yes ☐ Unknown	☐☐☐	☐ No ☐ Yes ☐ Unknown	☐☐☐
Sibling	☐ No ☐ Yes ☐ Unknown	☐☐☐	☐ No ☐ Yes ☐ Unknown	☐☐☐

If there is a history of stroke in one or more siblings, please enter the youngest age at which an event occured in ANY sibling. Similarly, where there is a history of MI, please insert the youngest age at which there was an event.

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SOUTH LONDON STROKE REGISTER ID Number

INITIAL FORM V19

19a. Does the patient smoke?

- ☐ Current smoker → Go to question 19c
- ☐ Ex-Smoker
- ☐ Never smoked → Go to question 20
- ☐ Unknown → Go to question 20

19b. If an ex-smoker, when did the patient give up?

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Month :	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Year: ☐ 1900 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9

☐ 2000 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9

19c. How old was the patient when they started smoking?

☐☐☐ years

19d. How much did/does the patient smoke a day?

Cigarettes (number) ☐☐☐

Tobacco (grams) ☐☐

Cigars (number) ☐☐

20a. Does the patient drink any alcohol?

- ☐ Yes
- ☐ No → Go to question 21
- ☐ Unknown → Go to question 21

20b. How much does the patient drink a week?

Beer (pints) ☐☐☐ Wine (glasses) ☐☐☐

Spirits (glasses) ☐☐☐

N.B. If the patient is an occassional drinker and drinks less than one unit per week, enter '0' in each of the three categories.

21a.How was the patient's weight obtained?

- ☐ Measured
- ☐ Recalled by patient
- ☐ Estimated
- ☐ Unknown → Go to question 21c
- ☐ Not done → Go to question 21c

21b. Patient's weight (k.g.) ☐☐☐.☐

21c. Patient's height (m) ☐.☐☐

MEDICATIONS PRIOR TO STROKE

22. Was the patient taking any regular medication in the month prior to stroke?

- ☐ Yes
- ☐ No → Go to question 24
- ☐ Unknown → Go to question 24

23. List all medications: (Generic Name)

	Name	Dose			Frequency		
A.		☐☐☐☐.☐☐	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other		☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
B.		☐☐☐☐.☐☐	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other		☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
C.		☐☐☐☐.☐☐	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other		☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
D.		☐☐☐☐.☐☐	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other		☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
E.		☐☐☐☐.☐☐	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other		☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other

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SOUTH LONDON STROKE REGISTER ID Number

INITIAL FORM V19

	Name	Dose		Frequency	
F.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
G.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
H.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
I.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
J.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
K.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
L.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
M.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
N.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
O.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other

N.B. If there are more than 15 medications, use 'extra medications' form and attach to back of this questionnaire.

STROKE ONSET AND SYMPTOMS

24. Date of stroke onset

Day: ☐☐ (10 20 30 0 1 2 3 4 5 6 7 8 9)

Month: ☐☐ (Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec)

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

25a. Time of first stroke symptom (24hr clock) ☐☐:☐☐ (h h : m m)

25b. Is the time of stroke definite?

☐ Yes → Go to question 26

☐ No

☐ Unknown → Go to question 26

25c. If no, did the patient wake up with the stroke?

☐ Yes

☐ No

☐ Unknown

26. Was the patient already in hospital at the time of stroke?

☐ Yes → Go to question 29

☐ No

☐ Unknown

27a. Was the patient seen in A&E?

☐ Yes

☐ No → Go to question 28

☐ Unknown → Go to question 28

27b. Date of arrival in A&E of first hospital .

Day: 10 20 30 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

27c. Time of arrival in A&E (24hr clock) h h : m m

28. Was the patient admitted to hospital?
- ☐ Yes
- ☐ No
- ☐ Unknown

STROKE SEVERITY (at time of maximum impairment)

29a. Is the level of consciousness (Glasgow Coma Scale) known?
- ☐ Yes
- ☐ No → Go to question 30
- ☐ Unknown → Go to question 30

29b. What was the GCS?

Eye
- ☐ 1 no eye opening
- ☐ 2 eye opening to pain
- ☐ 3 eye opening to speech
- ☐ 4 spontaneous eye opening

Verbal
- ☐ 1 None
- ☐ 2 Incomprehensible words
- ☐ 3 inappropriate wrods
- ☐ 4 confused conversation
- ☐ 5 orientated

Motor
- ☐ 1 No response
- ☐ 2 Extension to pain
- ☐ 3 abnormal flexor response to pain
- ☐ 4 withdraws from pain
- ☐ 5 localising response
- ☐ 6 obeying commands

30a. Swallow test results (by formal assessment)
- ☐ Fail
- ☐ Pass
- ☐ Not assessed → Go to question 31

30b. If *admitted*, was the test done within 24hrs post stroke admission?
- ☐ Yes → Go to question 31
- ☐ No → Go to question 31
- ☐ Unknown → Go to question 31

30c. If *not admitted*, was it done within 24hrs post stroke?
- ☐ Yes
- ☐ No
- ☐ Unknown

31. Has the patient been incontinent since the stroke?
- ☐ Yes
- ☐ No
- ☐ Unknown

32. Is the patient able to lift both arms to the horizontal?
(MRC score>2 in both arms)
- ☐ Yes
- ☐ No
- ☐ Unknown

33. Is the patient able to walk without the help of another person (can use stick/frame)?
- ☐ Yes
- ☐ No
- ☐ Unknown

34. Is the patient literate?

! *Information to be obtained directly from patient.* !
- ☐ Yes
- ☐ No
- ☐ Unknown

35. Is the patient right or left handed?

! *Information to be obtained directly from patient.* !
- ☐ Left
- ☐ Right
- ☐ Unknown

36.Stroke subtype
- ☐ Cerebral Infarction
- ☐ SAH
- ☐ PICH
- ☐ Undefined

Subtype should be defined by brain imaging, lumbar puncture (SAH only) or postmortem autopsy. If none of these investigations were performed, stroke subtype must be recorded as undefined

37. BARTHEL INDEX

	37a. Pre-Stroke status as at day before stroke	37b. Post-Stroke document status at day 5-10 or on discharge
	☐ Done ☐ Not done → Go to 37b ☐ Unknown → Go to 37b	☐ Done ☐ Not done → Go to 38 ☐ Unknown → Go to 38
FEEDING 0=unable 5=needs help cutting, spreading butter, etc., or requires modified diet 10=independent	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
BATHING 0 = dependent 5 = independent (or in shower)	☐ 0 ☐ 5	☐ 0 ☐ 5
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	☐ 0 ☐ 5	☐ 0 ☐ 5
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
TOILET 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	☐ 0 ☐ 5 ☐ 10 ☐ 15	☐ 0 ☐ 5 ☐ 10 ☐ 15
MOBILITY (ON LEVEL SURFACES) 0=immobile or <50 yards 5=wheelchair independent, including corners, >50 yards 10=walks with the help of one person (verbal or physical) >50 yards 15=independent (but may use any aid; for example, stick) >50 yards	☐ 0 ☐ 5 ☐ 10 ☐ 15	☐ 0 ☐ 5 ☐ 10 ☐ 15
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10

38. NIH STROKE SCALE

Document at time of maximum impairment

☐ Done
☐ Not done → Go to question 39
☐ Unknown → Go to question 39

1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	☐ 0 ☐ 1 ☐ 2 ☐ 3	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	☐ 0 ☐ 1 ☐ 2	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	☐ 0 ☐ 1 ☐ 2	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	☐ 0 ☐ 1 ☐ 2	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	☐ 0 ☐ 1 ☐ 2 ☐ 3	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	☐ 0 ☐ 1 ☐ 2 ☐ 3	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	RIGHT ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ UN LEFT ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ UN	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion

6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	RIGHT ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ UN LEFT ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ UN	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	☐ 0 ☐ 1 ☐ 2	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs.
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	☐ 0 ☐ 1 ☐ 2	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	☐ 0 ☐ 1 ☐ 2 ☐ 3	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	☐ 0 ☐ 1 ☐ 2 ☐ UN	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier.
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	☐ 0 ☐ 1 ☐ 2	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

39. MEMORY TESTING

☐ Done

☐ Not done → Go to question 40

☐ Unknown → Go to question 40

Document at 5-10 days post-stroke or on discharge

! *Information to be obtained directly from patient.* !

	Does patient answer correctly?	
1. How old are you?	☐ Yes	☐ No
2. What is the time (to the nearest hour, without looking at a clock)?	☐ Yes	☐ No
3. Please remember this address, you will be tested on it later on: ***42 West St.*** (the patient should recall the address to ensure it is heard correctly and then be tested on it in 5 minutes time; all parts must be recalled)	☐ Yes	☐ No
4. Which year are we in?	☐ Yes	☐ No
5. What is the name of the district that you are in?	☐ Yes	☐ No
6. a) What is my job? (You must ensure that you informed the patient initially) b) Can you name this object? (eg. a watch / pen / glasses) **(both parts must be answered correctly to score a point)**	☐ Yes	☐ No
7. What is your date of birth?	☐ Yes	☐ No
8. What was the date of the Second World War?	☐ Yes	☐ No
9. Can you name the present Monarch (Queen) ?	☐ Yes	☐ No
10. Can you start at 20 and count backwards?	☐ Yes	☐ No

Did the patient remember the address? (fill in question 3)

ACUTE INTERVENTIONS

40a.Was the patient on antiplatelet therapy in the first 14 days after stroke?

☐ Yes

☐ No

☐ Unknown

40b. If yes, which kind?

Aspirin	☐ Yes	☐ No	☐ Unknown	→ Go to question 41
Clopidogrel	☐ Yes	☐ No	☐ Unknown	→ Go to question 41
Other	☐ Yes	☐ No	☐ Unknown	→ Go to question 41

40c.If yes, was it given within 48hrs?

☐ Yes

☐ No

☐ Unknown

41a. Was the patient on anticoagulant drugs in the first 14 days after stroke?

☐ Yes

☐ No → Go to question 42

☐ Unknown → Go to question 42

41b.If yes, which types?

Oral	Intravenous	Subcutaneous
☐ Yes	☐ Yes	☐ Yes
☐ No	☐ No	☐ No
☐ Unknown	☐ Unknown	☐ Unknown

42.Was the patient given cholesterol lowering drugs in the first 14 days after stroke?

☐ Yes

☐ No

☐ Unknown

43a. Did the patient receive thrombolysis?

☐ Yes

☐ No → Go to question 44

☐ Unknown → Go to question 44

43b.If yes, which methods?

Intravenous	Intraarterial
☐ Yes	☐ Yes
☐ No	☐ No
☐ Unknown	☐ Unknown

44.Was the patient given intravenous fluids in the first 14 days after stroke?

☐ Yes

☐ No

☐ Unknown

45. Naso-gastric or PEG feeding in the first 14 days after stroke?

☐ Yes

☐ No

☐ Unknown

DISCHARGE INFORMATION

If the patient is still in hospital more than two weeks post stroke, please retain pages 10-12 for completion following discharge and return the rest of the form, complete, to the Stroke Office with the confidential discharge sheet.

46.Were any of the following interventional procedures done for the stroke? *Please select ALL relevant*

Stent	☐ Yes	☐ No	☐ Unknown
Coil	☐ Yes	☐ No	☐ Unknown
Tracheostomy	☐ Yes	☐ No	☐ Unknown
Evacuation	☐ Yes	☐ No	☐ Unknown
Craniectomy	☐ Yes	☐ No	☐ Unknown
Carotid Endarterectomy	☐ Yes	☐ No	☐ Unknown
Other	☐ Yes	☐ No	☐ Unknown

47. Was the patient seen by?

	1=No	2=Once	3=More than once	4=Unknown
Specialist physician in stroke medicine	☐ 1	☐ 2	☐ 3	☐ 4
Dietician	☐ 1	☐ 2	☐ 3	☐ 4
Psychologist	☐ 1	☐ 2	☐ 3	☐ 4
Social worker	☐ 1	☐ 2	☐ 3	☐ 4
Speech and language therapist	☐ 1	☐ 2	☐ 3	☐ 4
Occupational therapist	☐ 1	☐ 2	☐ 3	☐ 4
Physiotherapist	☐ 1	☐ 2	☐ 3	☐ 4

48. Since the stroke, has the patient been diagnosed with any of the following?

Hypertension	☐ No	☐ Yes	☐ Unknown
High Cholesterol	☐ No	☐ Yes	☐ Unknown
Atrial Fibrillation	☐ No	☐ Yes	☐ Unknown
Diabetes	☐ No	☐ Yes	☐ Unknown
Myocardial Infarction	☐ No	☐ Yes	☐ Unknown

BED MOVEMENTS

49ai. Date of admission to first ward

Day: ☐☐ (10 20 30) ☐☐ (0 1 2 3 4 5 6 7 8 9)

Month: ☐☐ (Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec)

Year ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital ☐ STH ☐ KCH ☐ STG ☐ UCLH ☐ LEW ☐ Other *Specify:* _____

49aii. Time of admission to first ward (24hr clock) ☐☐☐☐

49aiii. Type of ward first admitted to

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

49bi. Date of admission to second ward

Day: ☐☐ (10 20 30) ☐☐ (0 1 2 3 4 5 6 7 8 9)

Month: ☐☐ (Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec)

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital ☐ STH ☐ KCH ☐ STG ☐ UCLH ☐ LEW ☐ Other *Specify:* _____

49bii. Second ward type

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

49ci. Date of admission to third ward

Day: ☐☐ (10 20 30) ☐☐ (0 1 2 3 4 5 6 7 8 9)

Month: ☐☐ (Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec)

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital ☐ STH ☐ KCH ☐ STG ☐ UCLH ☐ LEW ☐ Other *Specify:* _____

49cii. Third ward type

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

49di. Date of admission to fourth ward

Day: ☐☐ (10 20 30) ☐☐ (0 1 2 3 4 5 6 7 8 9)

Month: ☐☐ (Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec)

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital ☐ STH ☐ KCH ☐ STG ☐ UCLH ☐ LEW ☐ Other *Specify:* _____

49dii. Fourth ward type

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

49ei. Date of admission to fifth ward

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: 2008 2009 2010 2011 2012 2013

Hospital: STH KCH STG UCLH LEW Other *Specify:*

49eii. Fifth ward type

Acute medical; Surgery; Neurosurgery; Other
Geriatric; Acute Stroke Unit; Private
ITU/HDU; Rehab Stroke Unit; Generic Rehab Unit

49fi. Date of admission to sixth ward:

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: 2008 2009 2010 2011 2012 2013

Hospital: STH KCH STG UCLH LEW Other *Specify:*

49fii. Sixth ward type

Acute medical; Surgery; Neurosurgery; Other
Geriatric; Acute Stroke Unit; Private
ITU/HDU; Rehab Stroke Unit; Generic Rehab Unit

DISCHARGE

50a. Date of discharge or death

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: 2008 2009 2010 2011 2012 2013

Hospital: STH KCH STG UCLH LEW Other *Specify:*

50b. Discharge destination

Private household alone; Nursing home; Residential home
Private household with carer; Private hospital; Death
Sheltered home; Community hospital; Other
Long term hospital care

51a. Did a stroke recurrence occur before discharge?

Yes
No → Go to question 52
Unknown → Go to question 52

51b. Date of first recurrence

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: 2008 2009 2010 2011 2012 2013

51c. Date of second recurrence

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: 2008 2009 2010 2011 2012 2013

52a. Did the patient receive any drugs as part of a trial?

Yes
No → Go to question 53
Unknown → Go to question 53

52b. If yes, specify:

MEDICATIONS AT DISCHARGE

53. List all medications prescribed on discharge or since stroke for non-admitted patients: (Generic Name)

	Name of drug	Dose		Frequency	
A.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
B.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
C.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
D.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
E.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
F.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
G.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
H.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
I.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
J.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
K.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
L.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
M.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
N.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
O.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable

N.B. If there are more than 15 medications, use 'extra medications' form and attach to back of this questionnaire.

Draft

SOUTH LONDON STROKE REGISTER

ID Number

INITIAL FORM V19

Interviewer ID

ECG

1a. Was an ECG performed?

☐ Yes

☐ No → Go to question 2

☐ Unknown → Go to question 2

1b. If yes was there any sustained arrythmia?

☐ Yes

☐ No → Go to question 2

☐ Unknown → Go to question 2

1c. If yes, what type?

☐ Atrial Fibrillation ☐ Sick sinus syndrome

☐ Atrial flutter ☐ Other

ECHO

2a. Was an ECHO performed?

☐ Yes → Go to question 2c

☐ No

☐ Unknown → Go to question 3

2b. If no, what was the reason?

☐ Haemorrhage ☐ Refused ☐ Not indicated

☐ Died ☐ Other *Specify:* Go to question 3

☐ Unable to contact

2c. If yes, what type?

☐ TTE ☐ Post mortem

☐ TOE ☐ Unknown

2d.If an ECHO was performed, were there any abnormal findings?

☐ Yes

☐ No → Go to question 3

☐ Unknown → Go to question 3

Please specify,

LA/atrial appendage thrombus	☐ No	☐ Yes	☐ Unknown	
Atrial myxoma	☐ No	☐ Yes	☐ Unknown	
Atrial septum aneurysum	☐ No	☐ 10-15mm	☐ >15mm	☐ Unknown
Patent foramen ovale	☐ No	☐ <5 bubbles	☐ 5-20 bubbles	☐ >20 bubbles ☐ Unknown
LVEF	☐ No	☐ <30%	☐ 30-50%	☐ >50% ☐ Unknown
LV thrombus	☐ No	☐ Mobile	☐ Non-mobile	☐ Unknown
Dilated cardiomyopathy	☐ No	☐ Yes	☐ Unknown	
LV segment	☐ Normal	☐ Akinetic	☐ Hypokinetic/Dyskinetic	☐ N/A ☐ Unknown
Nonbacterial thrombotic endocarditis	☐ No	☐ Yes	☐ Unknown	
Infective endocarditis	☐ No	☐ Yes	☐ Unknown	
Mechanical prosthetic valve	☐ No	☐ Aortic	☐ Mitral	☐ Unknown
Bioprosthetic valve	☐ No	☐ Aortic	☐ Mitral	☐ Unknown

VASCULAR IMAGING OF BRAIN SUPPLYING ARTERIES

3a. Were any vascular imaging tests perfomed?

☐ Yes → Go to question 3c

☐ No

☐ Unknown → Go to question 4

3b. If no, what was the reason?

☐ N/A ☐ Refused ☐ Not indicated

☐ Died ☐ Other *Specify:* Go to question 4

☐ Unable to contact

3c. If yes, which ones?

☑☐ *Please select ALL relevant answers*

☐ Doppler ultrasound ☐ MRA

☐ CTA ☐ Transcranial doppler

☐ Angiogram ☐ Other *Specify:*

☐ Duplex

3d. Was a relevant stenosis of the vessel(s)

☐ Yes

☐ No → Go to question 4

☐ Unknown → Go to question 4

3e. If yes, please document the estimated degree of stenosis as a percentage of the vessel(s)

R CCA	%	L CCA	%
R ICA	%	L ICA	%
R MCA	%	L MCA	%
R Posterior Circulation	%	L Posterior Circulation	%

3f. Other results of angiology

☑☐ *Please select ALL relevant answers*

☐ Dissection ☐ None

☐ Intracranial stenosis ☐ Other *Specify:*

☐ AVM

☐ Aneurysm

BLOOD INVESTIGATIONS

4a. Patients total cholesterol level

☐ Not done

☐ Unknown *state value* .

4b. Patients glucose level

☐ Not done

☐ Unknown *state value* .

4c. HbS (BLACK AFRICAN AND CARRIBEAN PATIENTS ONLY)

☐ Not present ☐ Not done
☐ Trait ☐ Unknown
☐ Heterozygous ☐ N/A

BRAIN IMAGING

5a. Were any of the following scans done?

	No	Yes, one	Yes, two	Yes, three	Yes, more than three	Unknown
CT	☐	☐	☐	☐	☐	☐
MRI	☐	☐	☐	☐	☐	☐
Angiography	☐	☐	☐	☐	☐	☐

5b. Date of first CT scan

Day: 10 20 30 ☐☐☐ 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐☐

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec ☐☐☐☐☐☐☐☐☐☐☐☐

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

5c. Date of first MRI scan

Day: 10 20 30 ☐☐☐ 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐☐

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec ☐☐☐☐☐☐☐☐☐☐☐☐

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

5d. Date of first angiography

Day: 10 20 30 ☐☐☐ 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐☐

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec ☐☐☐☐☐☐☐☐☐☐☐☐

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

RESULTS OF BRAIN IMAGING

6a. Localisation of stroke

☐ Location based on clinical signs ☐ No definite location
☐ Location based on imaging ☐ Unknown

	Right	Left	Both	Unknown
6b. ACA				
Cortex	☐	☐	☐	☐
6c MCA				
Cortex	☐	☐	☐	☐
Basal ganglia	☐	☐	☐	☐
6d. Posterior Circulation				
Cortex	☐	☐	☐	☐
Thalamus	☐	☐	☐	☐
Brainstem	☐	☐	☐	☐
Cerebellum	☐	☐	☐	☐

RESULTS OF 1st BRAIN IMAGING AFTER STROKE

7a. Estimated size of the lesion (when multiple lesions are present enter the size of the largest).

☐ No lesions ☐ 0.3-1.5cm ☐ Unknown
☐ <0.3cm ☐ >1.5cm

7b. Multiple lesions?

☐ No ☐ 2-4 ☐ >4 ☐ Unknown

7c. White matter lesions

☐ Yes ☐ No ☐ Unknown

RESULTS OF MOST RELEVANT DIAGNOSTIC SCAN

8a. Type of most relevant diagnostic scan?

☐ CT ☐ MRI ☐ Unknown

8b. Estimated size of the lesion (when multiple lesions are present enter the size of the largest).

☐ No lesions ☐ 0.3-1.5cm ☐ Unknown
☐ <0.3cm ☐ >1.5cm

8c. Multiple lesions?

☐ No ☐ 2-4 ☐ >4 ☐ Unknown

8d. White matter lesions

☐ Yes ☐ No ☐ Unknown

9. Date of most relevant diagnostic scan

Day: 10 20 30 ☐☐☐ 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐☐

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec ☐☐☐☐☐☐☐☐☐☐☐☐

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

STROKE CLASSIFICATION

10. OCSP Classification

☐ TACI ☐ LACI ☐ SAH
☐ PACI ☐ Infaction unspecified ☐ Unclassified
☐ POCI ☐ PICH ☐ Unknown

11. TOAST Classification (ISCHAEMIC STROKE ONLY)

Large artery atherosclerosis
☐ Extra-cranial
☐ Intra-cranial

Cardio-embolic
☐ High risk
☐ Medium risk

Small vessel occlusion
☐ Small vessel occlusion

Undetermined
☐ No aetiology identified
☐ Multiple probable aetiologies

Other determined
☐ Vasculopathy
☐ Haemoglobinopathy
☐ Hypercoagulable state
☐ Migrainious
☐ Other
Specify: _____

12. Modified TOAST Classification (ISCHAEMIC STROKE ONLY)

Large artery atherosclerosis
☐ Extra-cranial
☐ Intra-cranial

Cardio-embolic
☐ High risk
☐ Medium risk

Small vessel occlusion
☐ Small vessel occlusion

Undetermined
☐ No aetiology identified
☐ Multiple probable aetiologies

Other determined
☐ Vasculopathy
☐ Haemoglobinopathy
☐ Hypercoagulable state
☐ Migrainious
☐ Other
Specify: _____

APPENDIX 3. SLSR FOLLOW-UP FORM

SOUTH LONDON STROKE REGISTER
ANNUAL FOLLOW-UP

Thank you for taking time to complete this questionnaire. It will help us to know how you are getting on since your stroke.
Please read the following guidelines before beginning.
Answer all questions. We are well aware that some questions might not seem relevant to you personally, but please try to answer them all as best you can.
You should complete the form yourself, however if you are unable to then a carer or relative may help you.
Most questions require you to select your answer from choices given to you by selecting the box beside the *one* choice which best describes your situation /feelings.

1. What is today's date? Click here to enter a date.

2. What is your date of birth? Click here to enter a date.

3. Where do you live?

- ☐ Private household alone
- ☐ Private household with others
- ☐ Sheltered home
- ☐ Residential home
- ☐ Nursing home
- ☐ Community hospital
- ☐ Private hospital
- ☐ Long term hospital care
- ☐ Other

Specify: Click here to enter text.

4. What is your current employment status?

- ☐ Full time employed *(more than 30hrs/wk)*
- ☐ Part time employed *(less than 30hrs/wk)*
- ☐ Unemployed and looking for work
- ☐ Retired
- ☐ Unable to work due to disability/ill-health
- ☐ Carer for home/family/dependents

5a. Have you had another stroke in the last year?

☐Yes ☐No ☐I don't know

5b.Have you been readmitted to hospital since the last follow-up?

☐Yes ☐No →Go to question 6

5c.What was the name of the hospital?

Click here to enter text.

5d. Were you in hospital because you had had another stroke?

☐Yes ☐No ☐I don't know

---

6. In the last year have you experienced any of the following symptoms?

a. New visual problems ☐Yes ☐No ☐I don't know

c. New weakness of arms/legs ☐Yes ☐No ☐I don't know

b. New speech problems ☐Yes ☐No ☐I don't know

6d.If yes to any of the above, did you see your GP about the new symptoms?

☐Yes ☐No

7a. In the last 2 weeks, have you required help from another person for everyday activities (such as making a cup of tea)?

☐Yes ☐No →Go to question 8

7b. If yes, who did you receive most help from?

☐ Home help or carer
☐ Spouse/partner
☐ Daughter
☐ Son
☐ Other relative
☐ Friend
☐ Voluntary Organisation
☐ Other professional care (paid/unpaid)
☐ Other- Specify*:* Click here to enter text.

8. Has a member of your family given up work since the stroke to care for you?

☐ Yes ☐ No

---

9. Are you still in hospital, a nursing home, or a residential home?

☐ Yes →Go to question 17 ☐ No

---

10. Do your friends and family help you (at least once a week) with any of the following?

a. Cleaning the house	☐ Yes	☐ No
b. Preparing meals	☐ Yes	☐ No
c. Shopping	☐ Yes	☐ No
d. Having a bath or shower	☐ Yes	☐ No

---

11. In the last week have you had any meals on wheels? How many times?

☐ Yes ☐ No

→ **How many times?** ☐

---

12. In the last week have you had any home help?

☐ Yes ☐ No

→ **How many times?** ☐

---

13. In the last week have you attended a day centre?

☐Yes ☐No

→ **How many times?** ☐

---

14. In the last week have you attended a day hospital?

☐Yes ☐No

→ **How many times?** ☐

---

15. In the last week have you had a district nurse visit you?

☐Yes ☐No

→ **How many times?** ☐

---

16. In the last year, have you been admitted to a respite home for a short time to give yourself and your carer a rest?

☐Yes ☐No

17a. Have you had any physiotherapy in the last year?

☐Yes ☐No→Go to question 18

17b. Have you had this therapy in the last month?

☐Yes ☐No→Go to question 18

17c.Where was the therapy received?

☐Private ☐Acute stroke unit ☐Generic rehab unit
☐Geriatric ☐Acute Medical ☐Community rehab centre
☐ITU/HDU ☐Neurosurgery ☐Rehab at home team
☐Surgery ☐Rehab stroke unit ☐Other-

Specify: Click here to enter text.

18a. Have you had any occupational therapy in the last year?

☐Yes ☐No→Go to question 19

18b. Do you still have this therapy?

☐Yes ☐No→Go to question 19

18c.Where was the therapy received?

☐Private ☐Acute stroke unit ☐Generic rehab unit
☐Geriatric ☐Acute Medical ☐Community rehab centre
☐ITU/HDU ☐Neurosurgery ☐Rehab at home team
☐Surgery ☐Rehab stroke unit ☐Other-

Specify: Click here to enter text.

19a. Have you had any speech or language therapy in the last year?

☐Yes ☐No→Go to question 20

19b. Do you still have this therapy?

☐Yes ☐No→Go to question 20

19c. Where was the therapy received?

☐Private ☐Acute stroke unit ☐Generic rehab unit
☐Geriatric ☐Acute Medical ☐Community rehab centre
☐ITU/HDU ☐Neurosurgery ☐Rehab at home team
☐Surgery ☐Rehab stroke unit ☐Other-

Specify: Click here to enter text.

20a. Have you seen a GP in the last year?

☐Yes ☐No→Go to question 21

20b. Have you seen them in the last month?

☐Yes ☐No

How many times? ☐

21a. Have you seen a specialist hospital doctor in the last year?

☐Yes ☐No→Go to question 22

21b. Have you seen them in the last month?

☐Yes ☐No

How many times? ☐

22a. Have you seen a specialist nurse in the community in the last year?

☐Yes ☐No→Go to question 23

22b. Have you seen them in the last month?

☐Yes ☐No

How many times? ☐

23a. Has your blood pressure been checked in the last year?

☐Yes ☐No→Go to question 24

23b. When was your blood pressure checked?

☐Today ☐In the past week ☐1week-1month ago
☐1-6months ago ☐6-12months ago

23c. What was the most recent blood pressure?

Systolic ☐ **Diastolic** ☐ ☐I don't remember
(smaller number) (bigger number)

24. Do you currently have weakness or paralysis of a complete body side or an arm or a leg?

☐Yes ☐No ☐I don't know

25. Do you currently have slurred speech or problems talking to somebody because your mouth was unable to articulate words or sentences correctly?

☐Yes ☐No ☐I don't know

26. Do you currently have any trouble swallowing?

☐Yes ☐No ☐I don't know

27. Have you been diagnosed with any of the following in the last year?

Depression	☐Yes	☐No	☐I don't know
Hypertension	☐Yes	☐No	☐I don't know
High Cholesterol	☐Yes	☐No	☐I don't know
Diabetes	☐Yes	☐No	☐I don't know
Atrial fibrillation (Irregular heartbeat)	☐Yes	☐No	☐I don't know
Angina	☐Yes	☐No	☐I don't know
Peripheral vascular disease (narrowing of arteries in legs)	☐Yes	☐No	☐I don't know
Epilepsy	☐Yes	☐No	☐I don't know
Myocardial infarction (heart attack)	☐Yes	☐No	☐I don't know

Was it within the last month? ☐Yes ☐No

28. Have tried any of the following in the last year?

Cutting down on salt	☐Yes	☐No	☐ Don't Need to
Cutting down on fatty foods	☐Yes	☐No	☐ Don't Need to
Eating less to lose weight	☐Yes	☐No	☐ Don't Need to
Exercising to lose weight	☐Yes	☐No	☐ Don't Need to
Exercising to get fitter	☐Yes	☐No	☐ Don't Need to

29a.Do you smoke?

☐Yes ☐No→Go to question 29d

29b. If you are a smoker, how much do you smoke a day?

Cigarettes (number) ☐

Tobacco (grams) ☐

Cigars (number) ☐

29c.If you are a smoker, have you tried to cut down in the last year?

☐Yes ☐No

29d.If you are a non smoker now, are you an ex-smoker?

☐Yes ☐No→Go to question 30

29e.If you are an ex-smoker, have you given up in the last year?

☐Yes ☐No

30a. Do you drink any alcohol?

☐Yes ☐No→Go to question 31

30b. How much do you drink a week?

Beer (pints) ☐

Wine (glasses) ☐ ☐I don't drink every week

Spirits ☐

30c Have you cut down on the amount of alcohol you drink in the last year?

☐Yes ☐No ☐Tried but didn’t

---

31. Do you feel that you have made a complete recovery from the stroke?

☐Yes ☐No

---

32. Have you had any written information about preventing further strokes?

☐Yes ☐No ☐I don't know

---

33. Have you had any advice from your GP about preventing strokes?

☐Yes ☐No ☐I don't know

34a. Are you currently on any medication, including aspirin?

☐Yes ☐No→Go to question 35

34b. Please list all the medications you are currently taking in the spaces provided below

Name of Drug	Dose	How often do you take the drug? (Select from drop-down options)

Please answer yes or no to the following questions about support you receive from those around you

Is anyone helping you to complete the questions in this section?

☐ No, I am answering on my own
☐ Yes, my carer/family/friend is helping me
☐ I am a carer/family/friend answering on his/her behalf

---

1. If you needed help, do you have anyone (e.g. friends, neighbours, family) that you can turn to?

☐ Yes ☐ No

---

2. Do you have somebody (e.g. friends, neighbours, family) who shows that they care about you?

☐ Yes ☐ No ☐ I don't have any

---

3. Do you see as much of your neighbours as you would like?

☐ Yes ☐ No ☐ I don't have any

---

4. Do you see as much of your relatives as you would like?

☐ Yes ☐ No ☐ I don't have any

---

5. Do you see as much of your friends as you would like?

☐ Yes ☐ No ☐ I don't have any

On the following two pages are some questions about your ability to look after yourself. They may not all seem to apply to you but please answer them all by selecting *one* option which you feel best describes your situation.

Is anyone helping you to complete the questions in this section?

☐ No, I am answering on my own
☐ Yes, my carer/family/friend is helping me
☐ I am a carer/family/friend answering on his/her behalf

---

1. In the bath or shower, do you:

☐ manage on your own?
☐ need help getting in and out?
☐ need other help?
☐ need to be washed in bed?
☐ never have a bath or shower?

---

2. Can you climb stairs at home:

☐ without anyone's help?
☐ with someone encouraging you?
☐ with someone carrying your frame?
☐ with physical help?
☐ not at all?
☐ don't have stairs?

---

3. Do you get dressed:

☐ without any help?
☐ just with help with buttons?
☐ with someone helping you most of the time?

---

4. Do you walk indoors:

☐ without anyone’s help or with a frame?
☐ with one person watching over you?
☐ with one person helping you
☐ with more than one person helping you?
☐ not at all?
☐ or do you use a wheelchair independently(e.g round corners)

5. Do you move from bed to chair:

- ☐ on your own?
- ☐ with a little help from one person?
- ☐ with a lot of help from one or more people?
- ☐ not at all?

---

6. Do you eat food:

- ☐ without any help?
- ☐ with some help(such as cutting food or spreading butter)?
- ☐ with more help?

---

7. Do you use the toilet or commode:

- ☐ without anyone's help?
- ☐ with some help but can do some things?
- ☐ with quite a lot of help?

---

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

- ☐ without help?
- ☐ with help?

---

9. Do you lose control of your bladder? (are you incontinent of urine?):

- ☐ never
- ☐ less than once a week
- ☐ less than once a day
- ☐ more often
- ☐ or do you have a catheter managed for you?

---

10. Do you lose control of your bowel movements? (Do you soil yourself?):

- ☐ never
- ☐ occasional accident
- ☐ all the time

We are interested in finding out how often you carry out some activities. As you will see, the first page is about activities during the last *3 months* and over the page asks about the last *6 months*.
Please remember to select one box only for each question.

Is anyone helping you to complete the questions in this section?

☐ No, I am answering on my own
☐ Yes, my carer/family/friend are helping me
☐ I am a carer/family/friend answering on his/her behalf

In the last 3 months how often have you carried out these activities?

1. Preparing main meals (not just a snack)

☐ Never ☐ Less than once a week ☐ 1 or 2 times a week
☐ Most days

---

2. Washing up (Do all after one meal or share equally with another person)

☐ Never ☐ Less than once a week ☐ 1 or 2 times a week
☐ Most days

Over the last 3 months how often have you carried out these activities?

3. Washing clothes (e.g. loading and unloading washing machine)

☐ Never ☐ Only once or twice ☐ 1 to 4 times a month
☐ At least once a week

---

4. Light housework (e.g. dusting, or tidying small objects)

☐ Never ☐ Only once or twice ☐ 1 to 4 times a month
☐ At least once a week

---

5. Heavy housework (e.g. hoovering, or making beds)

☐ Never ☐ Only once or twice ☐ 1 to 4 times a month
☐ At least once a week

---

6. Local shopping

☐ Never ☐ Only once or twice ☐ 1 to 4 times a month
☐ At least once a week

---

7. Social occasions (including going to church)

☐ Never ☐ Only once or twice ☐ 1 to 4 times a month
☐ At least once a week

---

8. Walking outside for over 15 minutes

☐ Never ☐ Only once or twice ☐ 1 to 4 times a month
☐ At least once a week

---

9. Taking part in a hobby activity

☐ Never ☐ Only once or twice ☐ 1 to 4 times a month
☐ At least once a week

---

10. Going on a bus or driving a car

☐ Never ☐ Only once or twice ☐ 1 to 4 times a month
☐ At least once a week

In the last <u>6 months</u> how often have you carried out the following activities?

11. Travel outings or car rides (travel for pleasure, not just for routine trips)

☐ Never ☐ Only once or twice ☐ 1 to 2 times a month
☐ At least once a week

12.Gardening

☐ Never ☐ Light (e.g. occasional weeding) ☐ Moderate
☐ All necessary (Includes heavy digging)

---

13. Household or car maintenance

☐ Never ☐ Light (e.g. small repairs) ☐ Moderate (painting)
☐ All necessary

---

14. Reading books (not just magazines)

☐ Never ☐ One in 6 months ☐ Less than 1 a fortnight
☐ More than 1 a fortnight

---

15. Paid work

☐None ☐Up to 10hrs a week ☐10-30hrs a week
☐More than 30hrs a week

The following questions ask for your views about your health, how you feel and how well you are able to do your usual activities.
If you are unsure about how to answer any questions please give the best answer you can. Do not spend too much time in answering as your immediate response is likely to be the most accurate.

Is anyone helping you to complete the questions in this section?

☐No, I am answering on my own
☐Yes, my carer/family/friend are helping me
☐I am a carer/family/friend answering on his/her behalf.

---

1. In general, would you say your health is:

☐Excellent ☐Very Good ☐Good ☐Fair
☐Poor

---

2. Health and daily activities. The following questions are about activities you might do during a particular day. Does your health limit you in these activities? If so, how much?

A. Moderate activities (such as moving a table, pushing a vacuum, bowling or playing golf)

☐Yes, limited a lot
☐Yes, limited a little
☐No, not limited at all

B. Climbing several flights of stairs

☐Yes, limited a lot
☐Yes, limited a little
☐No, not limited at all

---

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Please answer Yes or No to each question)

A. Accomplished less than you would like

☐ Yes ☐ No

B. Were limited in the kind of work or other activities

☐ Yes ☐ No

---

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Please answer Yes or No to each question)

A. Accomplished less than you would like

☐ Yes ☐ No

B. Didn't do work or activities as carefully as usual

☐ Yes ☐ No

---

5. During the past 4 weeks how much did pain interfere with your normal work (including work both outside the home and housework)? (Please tick one box)

☐ Not at all ☐ A little bit ☐ Quite a bit ☐ Moderately ☐ Extremely

---

6. These questions are about how you feel and how things have been with you during the <u>past month</u>. For each question, please indicate the one answer that comes closest to the way you have been feeling. (Please tick one box)

How much time during the <u>last month</u>:

A. Have you felt calm and peaceful?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

B. Did you have a lot of energy?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

C. Have you felt downhearted and low?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

D. Has your health limited your social activities?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

This questionnaire is designed to help us know how you feel. Please give the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

Is anyone helping you to complete the questions in this section?

☐ No, I am answering on my own
☐ Yes, my carer/family/friend are helping me
☐ I am a carer/family/friend answering on his/her behalf

---

1. I feel tense or 'wound up':

☐ most of the time ☐ a lot of the time ☐ occasionally
☐ not at all

---

2. I feel as if I am slowed down:

☐ nearly all the time ☐ very often ☐ sometimes
☐ not at all

---

3. I still enjoy the things I used to:

☐ definitely as much ☐ not quite as much ☐ only a little
☐ hardly at all

---

4. I get a sort of frightened feeling like butterflies in my stomach:

☐ not at all ☐ occasionally ☐ quite often
☐ very often

---

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

☐ very definitely and quite badly ☐ yes, but not too badly
☐ a little, but it doesn't worry me ☐ not at all

---

6. I have lost interest in my appearance:

☐ definitely ☐ I don't take as much care as I should
☐ I may not take as much care as I should
☐ I take just as much care as ever

---

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

☐ as much as I always could ☐ definitely not so much now
☐ not quite so much now ☐ not at all

8. I feel restless as if I have to be on the move:

☐ very much indeed ☐ quite a lot ☐ not very much
☐ not at all

9. Worrying thoughts go through my mind:

☐ a great deal of the time ☐ a lot of the time
☐ from time to time ☐ only occasionally

10. I look forward with enjoyment to things:

☐ as much as I ever did ☐ definitely less than I used to
☐ rather less than I used to ☐ hardly at all

11. I feel cheerful:

☐ not at all ☐ not often
☐ sometimes ☐ most of the time

12. I get sudden feelings of panic:

☐ very often indeed ☐ quite often
☐ not very often ☐ not at all

13. I can sit at ease and feel relaxed:

☐ definitely ☐ usually ☐ not often
☐ not at all

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

☐ often ☐ sometimes ☐ not often
☐ very seldom

APPENDIX 4. SLSR CONSENT FORM

CONSENT FORM
South London Stroke Register

1. I have read and understand the information booklet date 20/02/2012 (version 2) about the South London Stroke Register and have had the opportunity to ask questions.

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 members of the research team will have access to my medical notes.

4. I agree to the researchers contacting my doctor or myself in future to obtain follow up information.

5. I agree to take part in the above research.

Name of patient _____

Signature _____ Date _____

Name of person taking consent _____

Signature _____ Date _____

Ethics Committee reference number: 01-195

Date of approval: 23/01/2008

Version 2

APPENDIX 5 DATA USED IN THE ANALYSES OF THE ASSOCIATION BETWEEN DEPRESSION AFTER STROKE AND DISABILITY AT FOLLOW-UP

	Age (years) n(%)		Gender n(%)		Ethnicity n(%)			
Disability	0-64	>64	Male	Female	White	Black	Other	Unknown
Year 1	654 (35.7)	1176 (64.3)	992 (54.2)	838 (45.8)	1273 (69.6)	419 (22.9)	121 (6.6)	17 (0.9)
2	474 (38.2)	767 (61.8)	672 (54.1)	569 (45.8)	842 (67.8)	302 (24.3)	83 (6.7)	149 (1.1)
3	506 (40.2)	751 (59.7)	709 (56.4)	548 (43.6)	870 (69.2)	286 (22.7)	83 (6.6)	18 (1.4)
4	449 (42.9)	598 (57.1)	566 (54.1)	481 (45.9)	701 (66.9)	255 (24.4)	77 (7.3)	14 (1.3)
5	362 (46.6)	415 (53.4)	434 (55.9)	343 (44.1)	525 (67.6)	181 (23.3)	62 (8.0)	9 (1.2)
6	327 (46.7)	373 (53.3)	392 (56.0)	308 (44.0)	476 (68.0)	168 (24.0)	51 (7.3)	5 (0.7)
7	267 (48.6)	282 (51.4)	313 (57.0)	236 (43.0)	367 (66.8)	139 (25.3)	36 (6.6)	7 (1.3)
8	251 (54.1)	213 (45.9)	271 (58.4)	193 (41.6)	298 (64.2)	128 (27.6)	32 (6.9)	6 (1.3)
9	201 (58.4)	143 (41.6)	202 (58.7)	142 (41.3)	231 67.1)	88 (25.6)	22 (6.4)	3 (0.9)
10	145 (58.2)	104 (41.8)	144 (57.8)	105 (42.2)	166 (66.7)	65 (26.1)	18 (7.2)	0
11	106 (54.1)	90 (45.9)	119 (60.7)	77 (39.3)	135 (68.9)	45 (23.0)	14 (7.1)	2 (1.0)
12	68 (58.6)	48 (41.4)	75 (64.7)	41 (35.3)	79(68.1)	28(24.1)	8 (6.9)	1 (0.9)
13	48 (64.9)	26 (35.1)	47 (63.5)	27 (36.5)	49(66.2)	22(29.7)	3 (4.0)	0
14	31 (64.6)	17 (35.4)	30 (62.5)	18 (37.5)	31(64.6)	14(29.2)	2 (4.2)	1(2.1)
15	8 (57.1)	6 (42.9)	6 (42.9)	8 (57.1)	9(64.3)	4(28.6)	0	1 (7.1)

	Depressed at 3 months n(%)			Depressed at 1 year n(%)			Depressed during year 1 n(%)		
Disability	No	Yes	Unknown	No	Yes	Unknown	No	Yes	Unknown
Year 1	567 (31.0)	271 (14.8)	992 (54.2)	871 (47.6)	346 (18.9)	613 (33.5)	807 (44.1)	503 (27.5)	520 (28.4)
2	426 (34.3)	206 (16.6)	608 (49.0)	556 (44.8)	212 (17.1)	472 (38.1)	547 (44.1)	342 (27.6)	351 (28.3)
3	382 (30.4)	170 (13.5)	705 (56.1)	542 (44.8)	178 (14.2)	537 (42.7)	535 (42.6)	279 (22.2)	443 (35.2)
4	309 (29.5)	140 (13.4)	598 (57.1)	439 (41.9)	140 (13.4)	468 (44.7)	431 (41.2)	226 (21.6)	390 (37.2)
5	231 (29.8)	104 (13.4)	441 (56.8)	315 (40.6)	92 (11.9)	369 (47.5)	310 (39.9)	155 (20.0)	311 (40.1)
6	189 (27.0)	84 (12.0)	427 (61.0)	271(38.8)	87 (12.4)	341 (48.8)	278 (39.7)	135 (19.3)	287 (41.0)
7	122 (22.2)	63 (11.5)	364 (66.3)	202 (36.8)	65 (11.8)	282 (51.4)	202 (36.8)	99 (18.0)	248 (45.2)
8	97 (20.9)	47 (10.1)	320 (69.0)	150 (32.3)	52 (11.2)	262 (56.5)	157 (33.8)	76 (16.4)	231 (49.8)
9	74 (21.5)	30 (8.7)	240(69.8)	110 (32.0)	36 (10.5)	198 (57.6)	114 (33.1)	53 (15.4)	177(51.4)
10	44 (17.7)	20 (8.0)	185 (74.3)	63 (25.3)	26 (10.4)	160 (64.3)	66 (26.5)	38 (15.3)	145 (58.2)
11	38 (19.4)	14 (7.1)	144 (73.5)	54 (27.5)	24 (12.2)	118 (60.2)	52 (26.5)	32 (16.3)	112(57.1)
12	14 (12.1)	11 (9.5)	91 (78.4)	30 (25.9)	15 (12.9)	71 (61.2)	25 (21.5)	20 (17.2)	71 (61.2)
13	0	0	74 (100)	13 (17.6)	5 (6.7)	56 (75.7)	13 (17.6)	5 (6.8)	56 (75.7)
14	1 (2.1)	0	47 (97.9)	1 (2.1)	0	47 (97.9)	1 (2.1)	0	47 (97.9)
15	0	0	14 (100)	0	0	14 (100)	0	0	14 (100)

Appendix 5. (Cont.)

	Paresis n(%)			Incontinence n(%)		
Disability	No	Yes	Unknown	No	Yes	Unknown
Year 1	424(23.2)	1238 (67.6)	168 (9.2)	1231 (67.3)	546(29.8)	53 (2.9)
2	328(26.4)	846(68.2)	67 (5.4)	861(69.4)	331(26.7)	49 (3.9)
3	338(26.9)	907(72.2)	12 (0.9)	868(69.0)	349(27.8)	40 (3.2)
4	293(28.0)	743(71.0)	11 (1.0)	730(69.7)	277(26.5)	40 (3.8)
5	231(29.7)	540(69.5)	6 (0.8)	571(73.5)	184(23.7)	22(2.8)
6	202(28.9)	489(69.9)	9 (1.3)	522(74.6)	150(21.4)	28 (4.0)
7	165(30.0)	375(68.3)	9(1.6)	401(73.0)	123(22.4)	25 (4.5)
8	142(30.6)	319(68.7)	3 (0.6)	345(74.3)	102(22.0)	17 (3.7)
9	106(30.8)	235(68.3)	3 (0.9)	262(76.2)	71 (20.6)	11 (3.2)
10	78 (31.3)	167(67.1)	4 (1.6)	185(74.3)	55 (22.1)	9 (3.6)
11	62 (31.6)	131(66.8)	3 (1.5)	144(73.5)	47 (24.0)	5(2.5)
12	31 (26.7)	84 (72.4)	1 (0.9)	82 (70.7)	31 (26.7)	3 (2.6)
13	14 (18.9)	60 (81.1)	0	53 (71.6)	20 (27.0)	1 (1.3)
14	8 (16.7)	40 (83.3)	0	37 (77.1)	11 (22.9)	0
15	3 (21.4)	11 (78.6)	0	12 (85.7)	2 (14.3)	0

Appendix 5. (Cont.)

	Glasgow coma score n(%)				Disability at baseline (Barhtel score) n(%)			
Disability	3-8	9-12	13-15	Unknown	0-14	15-19	20	Unknown
Year 1	71 (3.9)	153 (8.4)	1569 (85.7)	37(2.0)	758 (41.4)	330 (18.0)	503 (27.5)	239 (13.1)
2	42(3.4)	106 (8.5)	1052 (84.8)	41 (3.3)	468 (37.7)	209 (16.8)	356 (28.7)	208 (16.8)
3	51 (4.1)	102 (8.1)	1068 (85.0)	36 (2.9)	490 (39.0)	235 (18.7)	359 (28.6)	173 (13.8)
4	43 (4.1)	80 (7.6)	894(85.4)	30 (2.9)	383 (36.6)	189 (18.0)	316 (30.2)	159 (15.2)
5	29 (3.7)	58 (7.5)	671(86.4)	19 (2.4)	267 (34.4)	142 (18.3)	247 (31.8)	121(15.6)
6	27 (3.9)	47 (6.7)	606(86.6)	20 (2.9)	231 (33.0)	114 (16.3)	240 (34.3)	115 (16.4)
7	22 (4.0)	36 (6.4)	475(86.5)	17 (3.1)	181 (33.0)	93 (16.9)	181 (33.0)	94 (17.1)
8	21 (4.5)	34 (7.3)	399(86.0)	10 (2.2)	151 (32.5)	69 (14.9)	152 (32.8)	92 (19.8)
9	15 (4.4)	26 (7.6)	297(86.3)	6 (1.7)	107 (31.1)	55 (16.0)	120 (34.9)	62 (18.0)
10	14 (5.6)	18 (7.2)	212(85.1)	5 (2.0)	76 (30.5)	38 (15.3)	78 (31.3)	57 (22.9)
11	10 (5.1)	17 (8.7)	167(85.2)	2 (1.0)	64 (32.6)	29 (14.8)	60 (30.6)	43 (21.9)
12	7 (6.0)	10 (8.6)	97 (83.6)	2 (1.7)	50 (43.1)	21 (18.1)	38 (32.8)	7 (6.0)
13	5 (6.8)	7 (9.5)	61 (82.4)	1 (1.3)	33 (44.6)	16 (21.6)	22(29.7)	3 (4.0)
14	3 (6.2)	3 (6.2)	42 (87.5)	0	22 (45.8)	9 (18.7)	15 (31.2)	2 (4.2)
15	1 (7.1)	0	13 (92.9)	0	5 (35.7)	3 (21.4)	5 (35.7)	1 (7.1)

Appendix 5. (Cont.)

APPENDIX 6. DATA USED IN THE ANALYSES OF THE ASSOCIATION BETWEEN DEPRESSION AFTER STROKE AND COGNITION AT FOLLOW-UP

	Age (years) n(%)		Gender n(%)		Ethnicity n(%)			
Cognition	0-64	>64	Male	Female	White	Black	Other	Unknown
Year 1	508(37.0)	866(63.0)	756(55.0)	618(45.0)	965(70.2)	315(22.9)	80(5.8)	14(1.0)
2	387(38.5)	619(61.5)	548(54.5)	458(45.5)	691(68.7)	237(23.6)	66(6.6)	12(1.2)
3	360(40.0)	541(60.0)	513(56.9)	388(43.1)	612(67.9)	220(24.4)	57(6.3)	12(1.3)
4	321(43.0)	426(57.0)	406(54.3)	341(45.6)	508(68.0)	184(24.6)	47(6.3)	8(1.1)
5	305(48.1)	329(51.9)	356(56.1)	278(43.8)	427(67.3)	149(23.5)	50(7.9)	8(1.3)
6	258(48.0)	279(52.0)	304(56.6)	233(43.4)	371(69.1)	128(23.8)	33(6.1)	5(0.9)
7	203(50.6)	198(49.4)	233(58.1)	168(41.9)	279(69.6)	98(24.4)	21(5.2)	3(0.7)
8	167(52.7)	150(47.3)	189(59.6)	128(40.4)	219(69.1)	75(23.7)	21(6.6)	2(0.6)
9	147(57.6)	108(42.3)	150(58.8)	105(41.2)	180(70.6)	60(23.5)	13(5.1)	2(0.8)
10	94(56.6)	72(43.4)	95(57.2)	71(42.8)	115(69.3)	41(24.7)	10(6.0)	0
11	60(50.8)	58(49.1)	70(59.3)	48(40.7)	83(70.3)	30(25.4)	4(3.4)	1(0.8)
12	34(56.7)	26(43.3)	44(73.3)	16(26.7)	38(63.3)	18(30.0)	3 (5.0)	1(1.7)
13	20(69.0)	9(31.0)	21(72.4)	8(27.6)	18(62.1)	9(31.0)	2(6.9)	0
14	10(55.6)	8(44.4)	13(72.2)	5(27.8)	11(61.1)	6(33.3)	1(5.6)	0
15	4(50.0)	4(50.0)	2(25.0)	6(75.0)	5(62.5)	2(25.0)	1(12.5)	0

Appendix 6.

	Depressed at 3 months n(%)			Depressed at 1 year n(%)			Depressed during year 1 n(%)		
Cognition	No	Yes	Unknown	No	Yes	Unknown	No	Yes	Unknown
Year 1	455(33.1)	203(14.8)	716(52.1)	710(51.7)	249(18.1)	415(30.2)	655(47.7)	369(26.9)	350(25.5)
2	364(36.2)	189(18.8)	452(45.0)	481(47.9)	177(17.6)	347(34.5)	457(45.6)	294(29.2)	254(25.3)
3	313(34.7)	148(16.4)	440(48.8)	437(48.5)	140(15.5)	324(36.0)	428(47.5)	232(25.7)	241(26.7)
4	237(31.7)	127(17.0)	383(51.3)	364(48.7)	115(15.4)	268(35.9)	346(46.3)	194(26.0)	207(27.7)
5	169(26.7)	84(13.3)	380(60.0)	264(41.7)	71(11.2)	298(35.9)	263(41.5)	123(19.4)	247(39.0)
6	139(25.9)	64(11.9)	334(62.2)	214(39.9)	65(12.1)	257(47.9)	218(40.6)	103(19.2)	216(40.2)
7	89(22.2)	42(10.5)	270(67.3)	142(35.4)	44(11.0)	215(53.6)	142(35.4)	69(17.2)	190(47.4)
8	65(20.5)	33(10.4)	219(69.1)	101(31.9)	34(10.7)	182(57.4)	105(33.1)	52(16.4)	160(50.5)
9	48(18.8)	20(7.8)	187(73.3)	78(30.6)	25(9.8)	152(59.6)	77(30.2)	37(14.5)	141(55.3)
10	20(12.0)	8(4.8)	138(83.1)	41(24.7)	12(7.2)	113(68.1)	40(24.1)	17(10.2)	109(65.7)
11	14(11.9)	6(5.1)	98(83.0)	22(18.6)	11(9.3)	85(72.0)	19(16.1)	14(11.9)	85(72.0)
12	7(11.7)	6(10.0)	47(78.3)	15(25.0)	6(10.0)	39(65.0)	11(18.3)	10(16.7)	39(65.0)
13	0	0	29(100)	6(20.7)	3(10.3)	20(69.0)	6(20.7)	3(10.3)	20(69.0)
14	1(5.6)	17(94.4)	0	1(5.6)	0	17(94.4)	1(5.6)	0	17(94.4)
15	0	0	8(100)	0	0	8(100)	0	0	8(100)

Appendix 6. (Cont.)

	Paresis n(%)			Incontinence n(%)			Glasgow Coma score n(%)			
Cognition	No	Yes	Unknown	No	Yes	Unknown	3-8	9-12	13-15	Unknown
Year 1	354(25.8)	937(68.2)	83(6.0)	973(70.8)	359(26.1	42(3.1)	42(3.1)	91(6.6)	1212 (88.2)	29(2.1)
2	282(28.0)	689(68.5)	35(3.5)	722(71.8)	239(23.8)	45(4.5)	30(3.0)	66(6.6)	878(87.3)	32(3.2)
3	260(28.9)	631(70.0)	10(1.1)	649(72.0)	217(24.1)	35(3.9)	33(3.7)	52(5.8)	788(87.5)	28(3.1)
4	227(30.4)	510(68.3)	10(1.3)	556(74.4)	159(21.3)	32(4.3)	28(3.7)	43(5.8)	653(87.4)	23(3.1)
5	195(30.8)	435(68.6)	4(0.6)	477(75.2)	141(22.2)	16(2.5)	26(4.1)	46(7.3)	549(86.6)	13(2.0)
6	165(30.7)	366(68.2)	6(1.1)	419(78.0)	98(18.2)	20(3.7)	21(3.9)	32(6.0)	469(87.3)	15(2.8)
7	124(30.9)	271(67.6)	6(1.5)	307(76.6)	82(20.4)	12(3.0)	15(3.7)	20(5.0)	360(89.8)	6(1.5)
8	103(32.5)	212(66.9)	2(0.6)	249(78.5)	61(19.2)	7(2.2)	16(5.0)	17(5.4)	279(88.0)	5(1.6)
9	81(31.8)	173(67.8)	1(0.4)	198(77.6)	49(19.2)	8(3.1)	12(4.7)	14(5.5)	225(88.2)	4(1.6)
10	47(28.3)	117(70.5)	2(1.2)	127(76.5)	34(20.5)	5(3.0)	10(6.0)	9(5.4)	145(87.3)	2(1.2)
11	29(24.6)	87(73.7)	2(1.7)	91(77.1)	26(22.0)	1(0.8)	7(5.9)	7(5.9)	104(88.1)	0
12	19(31.7)	41(68.3)	0	46(76.7)	13(21.7)	1(1.7)	2(3.3)	3(5.0)	55(91.7)	0
13	5(17.2)	24(82.8)	0	22(75.9)	7(24.1)	0	3(10.3)	1(3.4)	25(86.2)	0
14	1(5.6)	17(94.4)	0	15(83.3)	3(16.7)	0	0	1(5.6)	17(94.4)	0
15	3(37.5)	5(62.5)	0	7(87.5)	1(12.5)	0	0	0	8(100)	0

Appendix 6. (Cont.)

	Glasgow Coma score n(%)				Disability at baseline (Barhtel score) n(%)			
Cognition	3-8	9-12	13-15	Unknown	0-14	15-19	20	Unknown
Year 1	42(3.1)	91(6.6)	1212 (88.2)	29(2.1)	513(37.3)	273(19.9)	413(30.1)	175(12.7)
2	30(3.0)	66(6.6)	878(87.3)	32(3.2)	342(34.0)	179(17.8)	310(30.8)	175(17.4)
3	33(3.7)	52(5.8)	788(87.5)	28(3.1)	300(33.3)	155(17.2)	294(32.6)	152(16.9)
4	28(3.7)	43(5.8)	653(87.4)	23(3.1)	236(31.6)	145(19.4)	239(32.0)	127(17.0)
5	26(4.1)	46(7.3)	549(86.6)	13(2.0)	215(33.9)	115(18.1)	200(31.5)	104(16.4)
6	21(3.9)	32(6.0)	469(87.3)	15(2.8)	164(30.5)	91(16.9)	193(35.9)	89(16.6)
7	15(3.7)	20(5.0)	360(89.8)	6(1.5)	128(31.9)	72(18.0)	131(32.7)	70(17.5)
8	16(5.0)	17(5.4)	279(88.0)	5(1.6)	99(31.2)	51(16.1)	97(30.6)	70(22.1)
9	12(4.7)	14(5.5)	225(88.2)	4(1.6)	80(31.4)	44(17.2)	92(36.1)	39(15.3)
10	10(6.0)	9(5.4)	145(87.3)	2(1.2)	54(32.5)	28(16.9)	57(34.3)	27(16.3)
11	7(5.9)	7(5.9)	104(88.1)	0	37(31.4)	25(21.2)	39(33.0)	17(14.4)
12	2(3.3)	3(5.0)	55(91.7)	0	25(41.7)	12(20.0)	19(31.7)	4(6.7)
13	3(10.3)	1(3.4)	25(86.2)	0	14(48.3)	6(20.7)	8(27.6)	1(3.4)
14	0	1(5.6)	17(94.4)	0	9(50.0)	3(16.7)	6(33.0)	0
15	0	0	8(100)	0	3(37.5)	0	4(50.0)	1(12.5)

Appendix 6. (Cont.)

APPENDIX 7. DATA USED IN THE ANALYSES OF THE ASSOCIATION BETWEEN DEPRESSION AND MENTAL HEALTH DOMAIN OF QUAILTY OF LIFE AT FOLLOW-UP

QoL	Age (years) n(%)		Gender n(%)		Ethnicity n(%)			
	0-64	>64	Male	Female	White	Black	Other	Unknown
Year 1	515(38.3)	828(61.7)	735(54.8)	607(45.2)	952(70.9)	306(22.8)	69(5.1)	15(1.1)
2	406(39.8)	614(60.2)	565(55.4)	455(44.6)	699(68.5)	246(24.1)	63(6.2)	12(1.2)
3	394(42.0)	544(58.0)	546(58.2)	392(41.8)	651(69.4)	213(22.7)	57(6.1)	17(1.2)
4	368(46.7)	420(53.3)	434(55.1)	354(44.9)	529(67.1)	195(24.7)	51(6.5)	13(1.6)
5	324(50.5)	317(49.4)	373(58.2)	268(41.8)	438(68.3)	146(22.8)	49(7.6)	8(1.2)
6	288(50.4)	283(49.6)	322(56.4)	249(43.6)	390(68.3)	146(22.8)	49(7.6)	8(1.2)
7	237(52.8)	212(47.2)	266(59.2)	183(40.8)	304(67.7)	111(24.7)	28(6.2)	6(1.3)
8	218(56.6)	167(43.4)	240(62.3)	145(37.7)	248(64.4)	106(27.5)	26(6.7)	5(1.3)
9	173(60.7)	11(39.3)	174(61.0)	11(38.9)	193(67.7)	70(24.6)	19(6.7)	3(1.0)
10	138(62.2)	84(32.8)	130(58.6)	92(41.4)	150(67.6)	70(24.6)	19(6.7)	3(1.0)
11	93(57.1)	70(42.9)	96(58.9)	67(41.1)	113(69.3)	37(22.7)	11(6.7)	2(1.2)
12	58(56.9)	44(43.1)	62(60.8)	40(39.2)	70(68.6)	25(24.5)	7(6.9)	0
13	39(66.1)	20(33.9)	36(61.0)	23(39.0)	39(66.1)	19(32.2)	1(1.7)	0
14	28(65.1)	15(34.9)	28(65.1)	15(34.9)	29(67.4)	11(25.6)	2(4.6)	1(2.3)
15	8(53.3)	7(46.7)	6(40.0)	9(60.0	10(66.7)	4(26.7)	0	1(6.7)

Appendix 7.

QoL	Depressed at 3 months n(%)			Depressed at 1 year n(%)			Depressed during year 1 n(%)		
	No	Yes	Unknown	No	Yes	Unknown	No	Yes	Unknown
Year 1	451(33.6)	191(14.2)	700(52.2)	750(55.9)	280(20.9)	312(23.2)	671(50.0)	386(28.8)	285(21.2)
2	376(36.9)	174(17.1)	469(46.0)	498(48.9)	179(17.6)	342(33.6)	478(46.9)	290(28.5)	251(24.6)
3	357(38.1)	143(15.2)	438(46.7)	474(50.5)	138(14.7)	326(34.7)	463(49.4)	230(24.5)	245(26.1)
4	292(37.1)	130(16.5)	366(46.5)	408(51.8)	117(14.8)	263(33.4)	393(49.9)	199(25.2)	196(24.9)
5	208(32.5)	93(14.5)	339(53.0)	290(45.3)	82(12.8)	268(41.9)	286(44.7)	141(22.0)	213(33.3)
6	168(29.4)	69(12.1)	334(58.5)	241(42.3)	70(12.3)	259(45.4)	249(43.6)	108(18.9)	214(37.5)
7	105(23.4)	58(12.9)	286(63.7)	180(40.1)	55(12.2)	214(47.7)	174(38.7)	89(19.8)	186(41.4)
8	91(23.6)	38(9.9)	256(66.5)	141(36.6)	40(10.4)	204(53.0)	147(38.2)	59(15.3)	179(46.5)
9	64(22.5)	24(8.4)	197(69.1)	99(34.7)	29(9.1)	160(56.1)	102(35.8)	42(14.7)	141(49.5)
10	40(18.0)	19(8.6)	163(73.4)	60(27.0)	19(8.6)	143(64.4)	64(28.8)	31(14.0)	127(57.2)
11	31(19.0)	15(9.2)	117(71.8)	46(28.2)	21(12.9)	96(58.9)	43(26.4)	28(17.2)	92(56.4)
12	14(13.8)	11(10.8)	77(75.5)	28(27.4)	14(13.7)	60(58.8)	23(22.5)	19(18.6)	60(58.8)
13	0	0	59(100)	11(18.6)	5(8.5)	43(72.9)	11(18.6)	5(8.5)	43(72.9)
14	1(2.3)	0	42(97.7)	192.3)	0	42(97.7)	1(2.3)	0	42(97.7)
15	0	0	15(100)	0	0	15(100)	0	0	15(100)

Appendix 7. (Cont.)

QoL	Paresis n(%)			Incontinence		
	No	Yes	Unknown	No	Yes	Unknown
Year 1	318(23.7)	866(64.5)	158(11.8)	980(73.0)	328(24.4)	34(2.5)
2	285(27.9)	676(66.3)	59(5.8)	750(73.5)	228(22.3)	42(4.1)
3	279(29.7)	648(69.1)	11(1.2)	678(72.3)	225(24.0)	35(3.7)
4	246(31.2)	530(67.3)	12(1.5)	589(74.7)	166(21.1)	33(4.2)
5	213(33.2)	423(66.0)	5(0.8)	490(76.4)	131(20.4)	20(3.1)
6	174(30.5)	390(68.3)	7(1.2)	441(77.2)	105(18.4)	25(4.4)
7	149(33.2)	292(65.0)	8(1.8)	347(77.3)	83(18.5)	19(4.2)
8	126(32.7)	256(66.5)	3(0.8)	299(77.7)	73(19.0)	13(3.4)
9	97(34.0)	187(65.6)	1(0.3)	227(79.6)	51(17.9)	7(3.1)
10	74(33.3)	145(65.3)	3(1.3)	173(77.9)	42(18.9)	7(3.1)
11	53(32.5)	107(65.6)	3(1.8)	125(76.7)	33(20.2)	5(3.1)
12	27(26.5)	74(72.5)	1(1.0)	70(68.6)	29(28.4)	3(2.9)
13	8(13.6)	51(86.4)	0	43(72.9)	15(25.4)	1(1.7)
14	6(13.9)	37(86.5)	0	33(76.7)	10(23.3)	0
15	3(20.0)	12(80.0)	0	13(86.7)	2(13.3)	0

Appendix 7. (Cont.)

QoL	Glasgow coma score n(%)				Disability at baseline (Barhtel score) n(%)			
	3-8	9-12	13-15	Unknown	0-14	15-19	20	Unknown
Year 1	41(3.1)	87(6.5)	1186 (88.4)	28(2.1)	493(36.7)	271(20.2)	431(32.1)	147(10.9)
2	29(2.8)	71(7.0)	886(86.9)	34(3.3)	344(33.7)	182(17.8)	331(32.4)	163(16.0)
3	33(3.5)	65(6.9)	808(86.1)	32(3.4)	318(33.9)	161(17.2)	305(32.5)	154(16.4)
4	26(3.3)	46(5.8)	690(87.6)	26(3.3)	239(30.3)	153(19.4)	276(35.0)	120(15.2)
5	21(3.3)	41(6.4)	560(87.4)	19(3.0)	200(31.2)	119(18.6)	226(35.3)	96(15.0)
6	23(4.0)	34(5.9)	498(87.2)	16(2.8)	174(30.5)	94(16.5)	209(36.6)	94(16.5)
7	19(4.2)	25(5.6)	393(87.5)	12(2.7)	138(30.7)	73(16.3)	166(37.0)	72(16.0)
8	18(4.7)	21(5.4)	340(88.3)	6(1.6)	120(31.2)	58(15.1)	135(35.1)	72(18.7)
9	15(5.3)	14(4.9)	253(88.8)	3(1.0)	82(28.8)	46(16.1)	112(39.3)	45(15.8)
10	14(6.3)	12(5.4)	194(87.4)	1(0.9)	55(24.8)	34(15.3)	75(33.8)	58(26.1)
11	8(4.9)	10(6.1)	143(87.7)	2(1.2)	48(29.4)	25(15.3)	53(32.5)	37(22.7)
12	7(6.9)	10(9.8)	83(81.4)	2(2.0)	46(45.1)	22(21.6)	30(29.4)	4(3.9)
13	5(8.5)	6(10.2)	47(79.7)	1(1.7)	29(49.1)	13(22.0)	14(23.7)	3(5.1)
14	3(7.0)	3(7.0)	37(86.0)	0	19(44.2)	9(20.9)	14(32.6)	1(2.3)
15	1(6.7)	0	14(93.3	0	5(33.3)	3(20.0)	6(40.0)	1(6.7)

Appendix 7. (Cont.)

APPENDIX 8. DATA USED IN THE ANALYSES OF THE ASSOCIATION BETWEEN DEPRESSION AND THE PHYSICAL DOMAIN OF QUALITY OF LIFE AT FOLLOW-UP

QoL	Age (years) n(%)		Gender n(%)		Ethnicity n(%)			
	0-64	>64	Male	Female	White	Black	Other	Unknown
Year 1	514(38.3)	828(61.7)	735(54.8)	607(45.2)	952(70.9)	306(22.8)	69(5.1)	15(1.1)
2	406(39.8)	614(60.2)	565(55.4)	455(44.6)	699(68.5)	246(24.1)	63(6.2)	12(1.2)
3	394(42.0)	544(58.0)	546(58.2)	392(41.8)	651(69.4)	213(22.7)	57(6.1)	17(1.8)
4	368(46.7)	420(53.3)	434(55.1)	354(44.9)	529(67.1)	195(24.7)	51(6.5)	13(1.6)
5	324(50.4)	317(49.4)	373(58.2)	268(41.8)	438(68.3)	146(22.8)	49(7.6)	8(1.2)
6	288(50.4)	283(49.6)	322(56.4)	249(43.6)	390(68.3)	138(24.2)	38(6.6)	5(0.9)
7	237(52.8)	212(47.2)	266(59.2)	183(40.8)	304(67.7)	111(24.7)	28(6.2)	6(1.3)
8	218(56.6)	167(43.4)	240(62.3)	145(37.8)	248(64.4)	106(27.5)	26(6.7)	5(1.3)
9	173(60.7)	112(39.3)	174(61.0)	111(38.9)	193(67.7)	70(24.6)	19(6.7)	3(1.0)
10	138(62.2)	84(37.8)	130(58.6)	92(41.4)	150(67.6)	56(25.2)	15(6.8)	1(0.4)
11	93(57.1)	70(42.9)	96(58.9)	67(41.1)	113(69.3)	37(22.7)	11(6.7)	291.2)
12	58(56.9)	44(43.1)	62(60.8)	40(39.2)	70(68.6)	25(24.5)	7(6.9)	0
13	39(66.1)	20(33.9)	36(61.0)	23(39.0)	39(66.1)	19(32.2)	1(1.7)	0
14	28(65.1)	15(34.9)	28(65.1)	15(34.9)	129(67.4)	11(25.6)	2(4.6)	1(2.3)
15	8(53.3)	7(46.7)	6(40.0)	9(60.0)	10(66.7)	4(26.7)	0	1(6.7)

Appendix 8

QoL	Depressed at 3 months n(%)			Depressed at 1 year n(%)			Depressed during year 1 n(%)		
	No	Yes	Unknown	No	Yes	Unknown	No	Yes	Unknown
Year 1	451(33.6)	191(14.2)	700(52.2)	750(55.9)	280(20.9)	312(23.2)	671(50.0)	386(28.8)	285(21.2)
2	376(36.9)	174(17.1)	469(46.0)	498(48.9)	179(17.6)	342(33.6)	478(46.9)	290(28.5)	251(24.6)
3	357(38.1)	143(15.2)	438(46.7)	474(50.5)	138(14.7)	326(34.8)	463(49.4)	230(24.5)	245(26.1)
4	292(37.1)	130(16.5)	366(46.4)	408(51.8)	117(14.8)	263(33.4)	393(49.9)	199(25.2)	196(24.9)
5	208(32.5)	93(14.5)	339(53.0)	290(45.3)	82(12.8)	268(41.9)	286(44.7)	141(22.0)	213(33.3)
6	168(29.4)	69(12.1)	334(58.5)	241(42.3)	70(12.3)	259(45.4)	249(43.6)	108(18.9)	214(37.5)
7	105(23.4)	58(12.9)	286(63.7)	180(40.1)	55(12.2)	214(47.7)	174(38.7)	89(19.8)	214(37.5)
8	91(23.6)	38(9.9)	256(66.5)	141(36.6)	40(10.4)	204(53.0)	147(38.2)	89(19.8)	214(37.5)
9	64(22.5)	24(8.4)	197(69.1)	99(34.7)	26(9.1)	160(56.1)	102(35.8)	42(14.7)	141(49.5)
10	40(18.0)	19(8.6)	163(73.4)	60(27.0)	19(8.6)	143(64.4)	64(28.8)	31(14.0)	127(57.2)
11	31(19.0)	15(9.2)	117(71.8)	46(28.2)	21(12.9)	96(58.9)	43(26.4)	28(17.2)	92(56.4)
12	14(13.7)	11(10.8)	77(75.5)	28(27.4)	14(13.7)	60(58.8)	23(22.5)	19(18.6)	60(58.8)
13	0	0	59(100)	11(18.6)	5(8.5)	43(72.9)	11(18.6)	5(8.5)	43(72.9)
14	1(2.3)	0	42(97.7)	1(2.3)	0	42(97.7)	1(2.3)	0	42(97.7)
15	0	0	15(100)	0	0	15(100)	0	0	15(100)

Appendix 8. (Cont.)

QoL	Paresis n(%)			Incontinence n(%)		
	No	Yes	Unknown	No	Yes	Unknown
Year 1	318(23.7)	866(64.5)	158(11.8)	980(73.0)	328(24.4)	34(2.5)
2	285(27.9)	676(66.3)	59(5.8)	750(73.5)	228(22.3)	42(4.1)
3	279(29.7)	648(69.1)	11(1.2)	678(72.3)	225(24.0)	35(3.7)
4	246(31.2)	530(67.3)	12(1.5)	589(74.7)	166(21.1)	33(4.2)
5	213(33.2)	423(66.0)	5(0.8)	490(76.4)	131(20.4)	20(3.1)
6	174(30.5)	390(68.3)	7(1.2)	441(77.2)	105(18.4)	25(4.4)
7	149(33.2)	292(65.0)	8(1.8)	347(77.3)	83(18.5)	19(4.2)
8	126(32.7)	256(66.5)	3(0.8)	299(77.7)	73(19.0)	13(3.4)
9	97(34.0)	187(65.6)	1(0.3)	227(79.6)	51(18.0)	7(2.5)
10	74(33.3)	145(65.3)	3(1.3)	173(77.9)	42(18.9)	7(3.1)
11	53(32.5)	107(65.6)	3(1.8)	125(76.7)	33(20.2)	5(3.1)
12	27(26.5)	74(72.5)	1(1.0)	70(68.6)	29(28.4)	3(2.9)
13	8(13.6)	51(86.4)	0	43(72.9)	15(25.4)	1(1.7)
14	6(13.9)	37(86.0)	0	33(76.7)	10(23.3)	0
15	3(20.0)	12(80.0)	0	13(86.7)	2(13.3)	0

Appendix 8. (Cont.)

QoL	Glasgow Coma score n(%)				Disability at baseline (Barhtel score) n(%)			
	3-8	9-12	13-15	Unknown	0-14	15-19	20	Unknown
Year 1	41(3.1)	87(6.5)	1186 (88.4)	28(2.1)	493(36.7)	271(20.2)	431(32.1)	147(10.9)
2	29(2.8)	71(7.0)	886(86.7)	34(3.3)	344(33.7)	182(17.8)	331(32.4)	163(16.0)
3	33(3.5)	65(6.9)	808(86.1)	32(3.4)	318(33.9)	161(17.2)	305(32.5)	154(16.4)
4	26(3.3)	46(5.8)	690(87.6)	26(3.3)	239(30.3)	153(19.4)	276(35.0)	120(15.2)
5	21(3.3)	41(6.4)	560(87.4)	19(3.0)	200(31.2)	119(18.6)	226(35.3)	96(15.0)
6	23(4.0)	34(5.9)	498(87.2)	16(2.8)	174(30.5)	94(16.5)	209(36.6)	94(16.5)
7	19(4.2)	25(5.6)	393(87.5)	12(2.7)	138(30.7)	73(16.3)	166(37.0)	72(16.0)
8	18(4.7)	21(5.4)	340(88.3)	6(1.6)	120(31.2)	58(15.1)	135(35.1)	72(18.7)
9	15(5.3)	14(4.9)	253(88.8)	3(1.0)	82(28.8)	46(16.4)	112(39.3)	45(15.8)
10	15(6.3)	12(5.4)	194(87.4)	2(0.9)	55(24.8)	34(15.3)	75(33.8)	58(26.1)
11	8(4.9)	10(6.1)	83(81.4)	2(1.2)	48(29.4)	25(15.3)	53(32.5)	37(22.7)
12	7(6.9)	10(9.8)	83(81.4)	2(2.0)	46(45.1)	22(21.6)	30(29.4)	4(3.9)
13	5(8.5)	6(10.2)	47(79.7)	1(1.7)	29(49.1)	13(22.0)	14(23.7)	3(5.1)
14	3(7.0)	3(7.0)	37(86.0)	0	19(44.2)	9(20.9)	14(32.6)	1(2.3)
15	1(6.7)	0	14(93.3)	0	5(33.3)	3(20.0)	6(40.0)	1(6.7)

Appendix 8. (Cont.)