Cerebrovascular Diseases, Vascular Risk Factors and Socioeconomic Status

A thesis by

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Abstract

Cerebrovascular disease, has an enormous, and increasing, impact on global health. As well as causing clinical stroke, cerebrovascular disease is thought to be a major contributor to cognitive decline and dementia. Socioeconomic status (SES) is associated with risk of stroke. Those in the lowest SES group are estimated to be at twice the risk of stroke compared to those in the highest SES group. Those with low SES may also have a more severe stroke and a poorer outcome. It is imperative that the extent and mechanism of this association is clarified.

This thesis aims to determine if the association between SES and stroke is explained by a greater prevalence of traditional vascular risk factors amongst those of low SES. It also explains the link with a novel risk factor, poor oral health. Lastly it addresses the long-term cognitive outcome in older people at risk of vascular disease.

A systematic review and meta-analysis was undertaken to establish if vascular risk factors explain the association between SES and stroke incidence / post-stroke mortality. This demonstrated that lower SES was associated with an increased risk of stroke and that a greater burden of vascular risk factors in those with low SES explained about 50% of the additional risk of stroke. However this meta-analysis could not clarify what vascular risk factors are most critical. Low SES was also associated with increased mortality risk in those who have a stroke although study results were heterogeneous and this link was not readily explained by known vascular risk factors.

A prospective study of 467 consecutive stroke and transient ischameic attack (TIA) patients from three Scottish hospitals was undertaken with the aim of establishing whether those with low SES carry higher levels of vascular risk factors, have a more severe stroke and have equal access to stroke care services and investigations. Stroke / TIA patients with low SES were younger and more likely to be current smokers but there was no association with other vascular risk factors /co-morbidity. Those who had lower SES had a more severe stroke. The lowest SES group were less likely to have neuroimaging or an electrocardiogram although differences were not significant on multivariate analysis. There was however equal access to stroke unit care.

A secondary analysis of a prospective cohort study of 412 stroke patients was conducted. The aim was to explore oral health after acute stroke and assess if poor oral health explains the association between SES and stroke. Dry mouth amongst acute stroke patients was very common, however there was no association between oral health and low SES. There was an association of dry mouth with pre-stroke disability and Urinary Tract Infection. There was also a link with oral *Candida glabrata* colonisation, although the clinical relevance of this is uncertain. In the acute phase after stroke there was no convincing association of dry mouth with dysphagia or pneumonia. Therefore there was no association between SES and poor oral health as measured in this study but oral health may still be part of the explanation of the association between SES and acute stroke and this needs further investigation.

Vascular disease is an important contributor to cognitive decline and dementia. Low SES may be associated with an increased risk of cognitive decline in later life and vascular disease may be a mediating factor. More effective prevention

of vascular disease may slow cognitive decline and prevent dementia in later life, particularly in low SES groups. Lipid lowering with statins might be effective in preventing dementia but so far evidence from randomised control trials does not show benefit from statins in preventing cognitive decline and dementia. However the duration of follow-up in these trials was short and there may be benefit in the long-term. My aim was therefore to establish if long-term follow-up of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study was feasible. I found that it was feasible to follow-up 300 elderly survivors from the Scottish arm of the PROSPER study and the methods could be extended to the whole group. As expected nearly half of the PROSPER participants were dead. Additionally a large proportion of traceable participants had significant cognitive impairment.

Smoking cessation, control of blood pressure and management of other vascular risk factors should be made a priority in areas of low SES. Additionally further research is needed to fully clarify the association between SES and stroke incidence. Avenues for exploration might include the possibilities of poorer access to effective stroke care, reduced uptake of care and poorer oral health in lower SES groups. In addition public health campaigns regarding smoking cessation should be directed at lower SES groups. I have shown that a large scale follow-up of the PROSPER participants is feasible and may determine new and novel risk factors for dementia and assess the long-term effect of a period of treatment with pravastatin.

Table of Contents

List of Tables

List of Figures

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Most importantly a huge thanks to the Kerr clan – I promise this will be the last time I ask anyone to have a 'quick look' for spelling mistakes.

Author's Declaration

The work described in this thesis was performed during my period as a Clinical Research Fellow in the Academic Section of Academic Medicine, Division of Cardiovascular and Medical Sciences, Faculty of Medicine, Glasgow University based at Glasgow Royal Infirmary.

The idea, design, organization, administration and writing-up of this thesis were performed by me with the advice of Professor David Stott and Professor Peter Langhorne, Glasgow University.

Helen Slavin (Geriatric ST5, Hairmyres Hospital), Donna Clark (Consultant Geriatrician, Perth Infirmary) and Professor Peter Langhorne were co-reviewers for the systematic review and meta-analysis detailed in Chapter 2. The data collection in Chapter 3 was done by me although I had assistance from the clinical staff of the respective Stroke Units. At Ayr Hospital the Stroke Unit ST2, Peter Higgins, was responsible for most of the inpatient data collection. Lynsey Bowie (former Research Speech and Language Therapist, Academic Section of Medicine, Glasgow University) collected the data for Chapter 4. The follow-up of the PROSPER study participants detailed in Chapter 5 was primarily done by myself with help from Melanie Shields (Research Nurse, Academic Section of Geriatric Medicine, Glasgow University). The statistical analysis in Chapter 5 was performed by Michelle Robertson of the Robertson Centre for Statistics, Glasgow University. All other statistical analysis and work was performed by me.

The original research contained within this Thesis was performed in accordance with the principles stated in the Declaration of Helsinki, and the conduct of the

research accorded to the principles of good clinical practice. Consent was obtained according to the requirements of the multi-centre and local research ethics committees. Management of all data was in compliance with the Data Protection Act.

Definitions / Abbreviations

AD	Alzheimer's Disease
ADL	Activities of Daily Living
AMT	Abbreviated Mental Test
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CRP	C-Reactive Protein
CT	Computerised Tomography
ECG	Electrocardiogram
EMBASE	Excerpta Medica Database
FEV1	Forced Expiratory Volume in 1 second
HDL	High Density Lipoprotein
HR	Heart Rate
GP	General Practitioner
IHD	Ischaemic Heart Disease
IADL	Instrumental Activities of Daily Living Scale
IL6	Interleukin-6
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	Interquartile Range
LVH	Left Ventricular Hypertrophy
MEDLINE	Medical Literature Analysis and Retrieval System Online
MI	Myocardial Infarction
MMSE	Mini Mental State Exam
mNIHSS	Modified National Institute of Health Stroke Scale
MRI	Magnetic Resonance Scan

mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
OAG	Oral Assessment Guide
OCSP	Oxfordshire Community Stroke Project
OR	Odds Ratio
PROSPER	The Prospective Study of Pravastatin in the Elderly at Risk
RR	Relative Risk
PVD	Peripheral Vascular Disease
SAH	Subarachnoid Haemorrhage
SBP	Systolic Blood Pressure
SD	Standard Deviation
SES	Socioeconomic Status
TACS	Total Anterior Circulation Stroke
TIA	Transient Ischaemic Attack
TICSm	Telephone Interview of Cognitive Status-modified
UTI	Urinary Tract Infection
VaD	Vascular Dementia
WST	Water Swallow Test

List of Relevant Presentations

Chapter 3

Kerr GD, Langhorne P, Stott DJ. Socioeconomic deprivation in acute stroke patients; a prospective cohort study. Platform Presentation at BGS Scotland Autumn Meeting 2008. Poster Presentation at UK Stroke Forum 2008. Abstract published in International Journal of Stroke.

Kerr GD, Langhorne P, Stott DJ. Socioeconomic deprivation is associated with higher levels of co-morbidity and adverse lifestyle factors in stroke patients. Poster Presentation at Royal College of Physicians and Surgeons of Glasgow Triennial Conference 2008.

Kerr GD, Higgins P, Lees KR, Walters MR, Ghosh SK, Wright F, Langhorne P, Stott DJ. Clinical features of acute stroke associated with low socioeconomic status. Poster Presentation at European Stroke Conference 2009. Abstract published in Cerebrovascular Diseases. Poster Presentation at UK Stroke Forum 2009. Abstract published in International Journal of Stroke.

Kerr GD, Higgins P, Walters MR, Ghosh SK, Wright F, Langhorne P, Stott DJ. Acute stroke service provision associated with low socioeconomic status. Platform Presentation at British Geriatric Society Spring Meeting 2010. Abstract published in Age & Ageing.

Chapter 4

Kerr GD, Bowie L, Sellars C, Bagg J, Sweeney MP, Langhorne P, Stott DJ. Dry mouth after stroke. Platform Presentation at British Geriatric Society Spring Meeting 2008. Abstract published in Age & Ageing.

Chapter 5

Kerr GD, Robertson M, Stott DJ. Long-term follow-up of the PROSPER study cohort: A feasibility study. Poster Presentation at British Geriatric Society Spring Meeting 2010. Abstract published in Age & Ageing.

List of Relevant Publications

Chapter 2

Kerr GD, Slavin H, Clark D, Coupar F, Langhorne P, Stott DJ. Do vascular risk factors explain the association between socioeconomic status and stroke incidence: a meta-analysis. Provisionally accepted at Cerebrovascular Diseases April 23rd 2010.

Chapter 3

Kerr GD, Higgins P, Walters M, Ghosh SK, Wright F, Langhorne P, Stott, DJ. Socioeconomic status and transient ischaemic attack / stroke: A prospective observational study. Submitted to Cerebrovascular Diseases March 28th 2010.

Chapter 4

Kerr GD, Sellars C, Bowie L, Bagg, J, Sweeney MP, Langhorne P, Stott DJ. Xerostomia after acute stroke. Cerebrovascular Diseases. 2009; 28: 624-626.

Chapter 5

Kerr GD, Robertson M, Stott DJ. Long-term follow-up of cognitive function and activities of daily living in older people; a feasibility study in the PROSPER cohort. Provisionally accepted at Clinical Trials May 7th 2010.

Chapter 1:

Introduction

Cerebrovascular Diseases

Stroke and Transient Ischaemic Attack

Stroke is defined by the World Health Organisation as a “sudden onset neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death or surgery within 24 hours" (1). The somewhat arbitrary 24 hour cut-off distinguishes stroke from transient ischaemic attack (TIA), where symptoms last for less than 24 hours. About 80% of strokes are caused by infarction and the remainder by haemorrhage (2). TIAs are very rarely due to haemorrhage.

Ischaemic stroke and TIA can be considered as a continuum of disease. TIA is by definition a self-limiting condition but it warns of potential complete stroke. The seven day risk of stroke following TIA may be more than a third in high risk groups (3) and up to 30% of patients with stroke give a history of preceding TIA (4).

Globally, stroke is the second most common cause of death in adults, heart disease being the leading cause (5). Stroke caused an estimated 5·7 million deaths in 2005 and the number of global deaths is projected to rise to 6·5 million in 2015 and to 7·8 million in 2030 (6). Worldwide, stroke is also a leading cause of disability.

In Scotland stroke is the third most common cause of mortality and the most common cause of disability (7). In 2009 there were 13,012 strokes in Scotland

with an incidence rate of 1.7/1,000 (8). Stroke also has dramatic economic burden. It is estimated that stroke cost the National Health Service 2.8 billion in 2005, more than the treatment of coronary heart disease, with an additional cost of 4.2 billion to the British economy (9).

Dementia

Dementia is a generic term indicating a loss of cognitive function including memory which can lead to a significant deterioration in the ability to carry out day to day activities, and often, changes in social functioning. Although usually slowly progressive there is no cure for dementia and it has a significant impact on sufferers and their cares. The prevalence of dementia is approximately 1.5% amongst 65-69 year olds but 30% in those aged over 90 (10). In Scotland in 2009 65,758 people are thought to have dementia but it is estimated that this will rise to 108,206 in 2029 (11).

The two most common causes of dementia are Alzheimer's disease (AD) and vascular dementia (VaD). They account for 75% of cases of dementia (11). Traditionally they were thought to be distinct entities with vascular dementia being caused by repeated small areas of cerebral infarction and Alzheimer's disease characterized by ß-amyloid deposition in brain parenchyma / blood vessels and by neurofibrillary tangles. This ß-amyloid deposition has a neurotoxic effect.

However VaD and AD share common vascular risk factors such as high blood pressure and diabetes (12;13). It is now known that in AD there is dysregulation

of cerebral blood flow due to the ß-amyloid deposition and vascular risk factors may exaggerate this response to ß-amyloid. In addition ß -amyloid production is increased by cerebral ischaemia (14). ß -amyloid and neurofibrillary tangles have been found in cases of what were thought to be vascular dementia and also in post-stroke dementia. The distinct division between VaD and AD has become increasingly blurred and many subjects with dementia have a combination of these pathologies (15).

Clinical stroke is associated with dementia. A 2009 meta-analysis (16) demonstrated that 10% of acute stroke patients go on to develop dementia soon after stroke, additionally a third will develop dementia after recurrent stroke. The increase of new-onset dementia shortly after stroke indicates that the stroke itself had a substantial and immediate effect on the absolute rate of dementia that was in addition to the risk from pre-existing vascular risk factors.

Socioeconomic Status

Socioeconomic status (SES) is an individual's position relative to others, based on income, education and occupation. However the term socioeconomic status can be used with somewhat different meanings. It can be used to refer to social class or to the individual components of SES; income or poverty, education and occupation.

Differences in SES are associated with large inequalities in health status (17;18) and reduced SES is related to both increased morbidity (19) and mortality (20). The disparities are seen with all of the individual components of SES although the effects are largest for poverty (21).

As well as the differing nomenclature surrounding SES analysing the evidence of a link between SES and health is complicated by the different SES measures used. Additionally the effects of low SES at different points in the life cycle (in utero, childhood, adulthood) have different health outcomes. This will be discussed in the next section.

Measuring Socioeconomic Status

There is no consensus on the "best" measure of SES and the choice of which to use may be a pragmatic one. However the variable use of different measures can make it difficult to compare evidence.

Education is frequently used a measure of SES and is comparatively easy to measure either as continuous variable (years of education) or categorical variable (completion of secondary education, higher education) (22). However as numbers continuing in education have increased in recent years it may problematic to use education to measure changes in SES over time (23). Additionally simply measuring the length of education does not quantify the quality or qualifications gained.

Occupation has traditionally been used as a measure of SES and social class, and is available in census information. However the major drawback is the question of how should those who are retired, self-employed, unemployed and studying be classified. In the past women have often been classified based on their husband's occupation, but this in no longer relevant in modern society. In addition the workforce has changed with more people in service and information technology jobs; these are difficult to classify (24).

Income may be the component of SES most strongly correlated with health (21) and as such it has advantages over education and occupation. However people are more reluctant to divulge information about their salary (25) and salary can fluctuate in the short-term.

Partly because of the criticisms of single, individual measure of SES there has been increasing interest in small area SES statistics, in addition these composite measures can easily be generated from census data. Small area SES is not just a substitute for individual SES as there is increasing evidence that area-based SES is an independent predictor of mortality (26).

The Carstairs Deprivation Index (27) was developed for Scotland and is based on four census indicators: low social class, lack of car ownership, overcrowding and male unemployment. More recently in Scotland the Scottish Government has developed the Scottish Neighbourhood Statistics Programme (28). This uses information on education, employment, environment, health, housing, crime and services to generate small area statistics on SES. It provides an index of SES for each Scottish post code from 1 (lowest SES) to 6505 (highest SES). About a thousand people live in each of these post code areas. Scottish Neighbourhood Statistics are used as the measure of SES in Chapters 3 and 4 of this thesis.

Small area statistics can also be criticised. There may be a misclassification or false interpretation of an individual's SES because of assumptions about the area. An area may not be internally consistent with a wide variation of individual SES, but the smaller the area the less likely this is to occur.

SES can also be considered at different stages of life. For some diseases childhood SES is more critical. An example is the link between childhood SES and gastric cancer, likely to be due to childhood infection with *Helicobacter Pylori* (29). Adult SES is linked to poor health because of accidents and violence (30) whereas the link between SES and ischaemic heart disease appears to depend on life-time SES (31;32).

SES is a complex concept with variable measurements and is not fixed throughout an individual's life. Despite these complexities SES is key to resolving ongoing health inequality.

Socioeconomic Status and Stroke

There is a long established link between poor cardiovascular health (33-35) and low SES but it has not been until more recently that evidence has emerged regarding the possible link between SES and stroke.

Stroke Incidence

The heterogeneous methodology / measurement of SES and the relatively small amount of current evidence make it difficult to draw conclusions about SES and stroke. However there is consistently emerging evidence of increased stroke incidence amongst those of low SES (36-42;42-52).

The most recently published large scale study undertaken in Europe (51) looked at 10,033 strokes and demonstrated that those in the lowest SES group were at nearly twice the risk of ischaemic stroke compared to those in the highest SES group, for men the relative risk (RR) was 1.76 (95% confidence interval (CI) 1.59-1.95) and for women 1.72 (95% CI 1.55-1.91). In 2007 Kuper et al (38) considered 47,942 middle aged women and determined that those in the lowest SES group were at twice the risk of stroke (hazard ratio (HR) 2.1, 95% CI 1.4-2.9).

McFadden et al (52) undertook a prospective population study of 22,488 men and women in the UK. This cohort was followed-up to 2007 when there had been 683 incident strokes. Those in the lowest SES group were more than twice as likely to have a stroke (HR 2.62. 95% CI 1.63-4.22).

These three studies considered both fatal and non-fatal stroke, as have most studies considering stroke incidence. Three studies have considered fatal stroke only (36;53;54) but have demonstrated similar increased risk to the studies that consider both non-fatal and fatal stroke. It is not yet clear if there would be a difference in the association of SES and non-fatal / fatal stroke.

Additionally all stroke etiology is generally considered together. Cesaroni et al (51) provided separate figures for ischaemic and haemorrhagic stroke. For men the risk of haemorrhagic stroke in the lowest SES group compared to the highest SES group was RR 1.5 (95% CI 1.26-1.8) and for women, RR 1.37 (95% CI 1.15-1.63). Jakovljevic et al (55) undertook a study considering only haemorrhagic stroke and SES. The risk of haemorrhagic stroke in the lowest SES group was odds ratio (OR) 2.12 (95% CI, 1.02-4.4).

Therefore despite the methodological heterogeneity of studies there appears to be a consistent association between low SES and increased stroke incidence.

Stroke Severity and Outcome

Those from lower SES groups may have more severe neurological impairment (56-59) although this has been considered in relatively few studies and all considered hospital inpatients only. There were both variable measures of stroke severity and SES used in these four studies. Arrich et al (56) used the National Institute of Health Score (NIHSS) to assess stroke severity and the lowest income group had a score of 5 (interquartile range (IQR) 2-7) compared to 3 (IQR 1-6) in the highest income group.

There is also some limited evidence that those stroke patients with low SES have a greater likelihood of disability (45;59;60). Only Sturm et al (60) specifically looked at post-stroke disability, the other two studies considered disability in a secondary analysis. Sturm el al (60) did not demonstrate that SES was an independent predictor of disability.

There is some evidence to suggest that those with a lower SES have increased post-stroke mortality (45;55;56;61-63). However only two of these six studies clearly adjusted for stroke severity. Kapral et al (61) was one and showed an increased risk of post-stroke mortality in both the short (30 days) and long term (1 year) when income or occupation were used as measure of SES, but not when education was used. Zhou et al (62) considered post-stroke mortality at three years and found that there was an increased risk for those of lower SES when measured by income, occupation and housing space but not education. Several other studies report no significant association (47;51;57;58;64), including the recent Cesaroni et al (51).

There is also no conclusive evidence on whether those with low SES are more likely to need long term care after their stroke. Two studies from the UK found no increased risk of long term care (57;58) but the opposite conclusion was made by two European studies (45;59). However the provision and expectation of long term care is partly culturally driven and it is perhaps not surprising that results differ between countries.

Therefore, in summary, currently it is difficult to draw any firm conclusion on whether low SES may lead to more severe stroke or a poorer post-stroke outcome.

Vascular Risk Factors

It is known that there is a greater burden of vascular risk factors, such as hypertension and diabetes, amongst those of low SES (65-67) and it has been proposed that this may explain the association between SES and stroke incidence. A greater burden of vascular risk factors in lower SES groups of stroke patients has been shown in some studies of stroke incidence (36;38-41;44;53;68) however van Rossum et al showed no association with vascular risk factors (49). Additionally, a recent study by McFadden et al (52) found that none of the classical vascular risk factors explain the association between stroke and SES.

Despite this there does seem to be growing evidence that increased vascular risk factors amongst low SES stroke patients is part of the explanation of the association between SES and stroke. However it is not clear which vascular risk factor are most critical. Most of the studies consider several or grouped vascular risk factors and no clear picture is emerging.

Access to Health Care

It is known that provision of stroke care varies (69;70) and it has been postulated that low SES stroke patients may not have equitable access to health care. There have been few studies looking at multiple aspects of stroke provision and SES and there is no consensus. McKevitt et al (71) found no socioeconomic inequality in stroke provision although Jakovlijevic et al (45) found that lower

SES patients were less likely to have appropriate imaging, see a specialist and be treated in a university hospital. There are other studies which consider single aspects of stroke care. Those with positive results were Maclead et al (72) who demonstrated that stroke patients with a low SES took longer to reach hospital in Edinburgh. In the Netherlands it was found that 3 months after stroke low SES patients were less likely to receive secondary prevention (73).

Therefore the theory that those in lower SES groups have restricted access to stroke health care is plausible and interesting but needs further exploration.

Early-life Influences

The in-utero hypothesis explains the link between SES and stroke by proposing that under nutrition in-utero, and early childhood, is related to stroke in later life. It has been shown that people with low birth weight are at higher risk of stroke as adults (74;75). It is proposed that poor growth in utero is linked to the development of hypertension because of damage to vasculature secondary to poor nutrition. This theory is largely unproven in stroke.

Socioeconomic Status, Stroke and Oral Health

Poor oral health and in particular periodontitis (inflammatory disease affecting the tissues that surround and support the teeth) is an established risk factor for stroke (76-79). Dorfer et al (76) found a 7.4 times (95% CI 1.55–15.3) risk of ischaemic stroke amongst patients with periodontitis compared to those without. While Wu et al (78) found a 2.1 times (95% CI 1.30-3.42) risk of ischaemic stroke in those who had periodontitis, although when both ischaemic strokes and haemorrhagic strokes were considered the risk for those with periodontitis was no longer significant, 1.23 (95% CI 0.91-1.66). The mechanism may be the known link between the local or systemic infection / inflammation and atherosclerosis (80).

Low SES is linked to poor oral health including periodontitis (81;82). It is theorised that dental disease might be part of the explanation for the association between stroke and SES although there is currently no evidence to confirm or refute this.

Socioeconomic Status and Dementia

There is an established association between lower levels of education and increased risk of cognitive impairment and dementia (83;84). However this is due in part to the known correlation of education with cognitive test performance at all ages. Additionally education is likely to contribute to “brain reserve”. This is a multifactorial phenomena related to complex brain activity which allows preserved cognitive function despite underlying pathology. Those

with greater occupational complexity, late-life mental activity and higher levels of education are likely to have a greater capacity to preserve cognitive function despite neurodegenerative pathology (85). It is therefore considered problematic to use education as a measure of SES when considering cognitive impairment.

There is also some evidence of an association between increased risk of cognitive impairment / dementia and low SES, measured by income (86-88) and occupation (89). Recently a large study (90) of 13,004 men and women aged over 65 considered the association of SES, measured by small area statistics (Townsend deprivation score), and cognitive impairment (mini-mental state exam <21). Those in the lowest quintile of SES were more than twice as likely (OR 2.3; 95% CI 1.8–3.0, $p<0.001$) to be cognitively impaired compared to those in the highest quintile of SES after controlling for age, sex and education.

There has also been interest between the association of late life cognitive impairment / dementia and childhood SES. There is evidence to suggest a link between reduced cognitive function in adulthood and low SES in childhood (91;92) but two studies have failed to show a link between cognitive impairment / dementia and childhood SES (93;94).

Cerebrovascular Disease Prevention

Stroke

Stroke prevention involves multiple strategies including the use of antiplatelets, anticoagulation and carotid artery intervention. However, the focus of this section will be the treatment of the classical vascular risk factors; hypertension, raised cholesterol, diabetes and smoking.

Hypertension

Treating hypertension is known to be effective in primary prevention of stroke (95). Hypertension treatment is also known to be effective secondary prevention. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial (96) considered 6105 stroke patients. Treatment with either perindopril or a combination of perindopril and indapamide led to a 28% relative risk reduction (95% CI 17 to 38%) of recurrent stroke. Benefits were similar regardless of diagnosis of hypertension and the average blood pressure at the start of the trial was 147/86 mmHg. This suggests that normotensive stroke patients may also benefit from lowering blood pressure. A 2006 meta-analysis (97) has shown that lowering the blood pressure after stroke reduces the odds of recurrent stroke by 24% (OR 0.76, 95% CI 0.63-0.92).

The treatment of hypertension and blood pressure lowering is therefore a priority in both primary and secondary prevention of stroke.

Raised Cholesterol

There is ongoing debate about the link between raised cholesterol and stroke. However statin therapy is routinely recommended in ischaemic stroke (7). There is compelling evidence that treatment with statins is effective primary prevention of ischaemic stroke. The 2002 Heart Protection Study (HPS) (98) enrolled 20,536 patients with ischaemic heart disease (IHD) or vascular risk factors and compared simvastatin with placebo. Simvastatin reduced the risk of first stroke by 25% (95% CI 15% to 34%). A later meta-analysis (99) of over 90000 patients (mostly with IHD) demonstrated that statin treatment significantly reduced the risk of incident stroke (OR 0.79, 95% CI 0.73-0.85).

However in the HPS (98) a sub-group analysis of patients who had a previous stroke showed that statin therapy did not reduce recurrence. This suggested that statin was not useful in the secondary prevention of stroke. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (100) randomised 4731 patients to high dose atorvastatin or placebo. Treatment led to a 16% relative risk reduction (HR 0.84, 95% CI 0.71 to 0.99) of recurrent stroke. These results demonstrate that statin therapy may reduce recurrent stroke.

There is a suggestion that the marginal benefit of statin therapy in secondary prevention of stroke may be due to the fact that statins increase the risk of

haemorrhagic stroke. Vergouwen et al (101) conducted a recent meta-analysis of statin therapy as secondary prevention of stroke. Four studies were included investigating the effect of statins in 8832 patients with a history of stroke. The pooled relative risk for statin users of overall stroke during follow-up was 0.88 (95% CI: 0.78 to 0.99). The pooled relative risk of ischemic stroke was 0.80 (95% CI: 0.70 to 0.92) and of hemorrhagic stroke 1.73 (95% CI: 1.19 to 2.50).

Currently statin therapy is recommended after ischaemic stroke but is not generally used after haemorrhagic stroke.

Diabetes

Diabetes is a risk factor for stroke (102;103) and recurrent stroke (104) but successive large randomised controlled trials have failed to show the benefit of tight glycaemic control on macrovascular events including stroke (105-107). However these trials have shown a reduction in microvascular complications (retinopathy, nephropathy and neuropathy).

Neither the Scottish Intercollegiate Guideline Network (7) or American Heart Association / American Stroke Association (108) make any current recommendations about diabetes treatment to prevent stroke, nor recurrent stroke.

Smoking

Cigarette smoking is a risk factor for both stroke and recurrent stroke (109) and it has been shown that cigarette smoking leads to twice the risk of ischaemic stroke (110). There is no randomised control trial evidence to evaluate smoking cessation therapy after stroke as it is regarded as critical given the other health benefits associated with stopping. Observational data suggests that smoking cessation reduces stroke risk and that risk returns to that of a non-smoker after 5 years (111).

Dementia

Given the importance of cerebrovascular disease as a contributor to dementia, it is plausible that active treatment of classical vascular risk factors might be effective as a strategy for preventing dementia.

Hypertension

Several studies have shown that hypertension is associated with increased risk of dementia later in life (13;112;113). Extended follow-up of the Systolic Hypertension in Europe Study (Sys Eur) suggested that treatment of systolic hypertension protected against dementia. Patients in this study were at least 60

and had a Systolic Blood Pressure (SBP) of >160. They were followed up for 4 years and the 1417 control subjects had a SBP that was 7mmHg higher then the 1485 treated subjects at the end of that period. The risk of dementia was reduced by 55% in the treated group, from 7.4 to 3.3 cases per 1000 patient years. However there was a low incidence of dementia in this study with only 64 cases diagnosed.

However a Cochrane Review of three trials comprising 12 091 hypertensive individuals found no convincing evidence that lowering blood pressure prevented dementia (114). The Hypertension in the Very Elderly Trial cognitive function trial (HYVET-COG) examined 3336 hypertensive patient aged over 80. The mean decrease in SBP between the treatment and placebo groups at 2 years was systolic 15 mm Hg. There were 263 incident cases of dementia. The rates of incident dementia were 38 per 1000 patient-years in the placebo group and 33 per 1000 patient-years in the treatment group. There was no significant difference between treatment and placebo groups (HR 0·86, 95% CI 0·67–1·09).

At present there is not consistent evidence to suggest that treating hypertension reduces the risk of dementia.

Raised Cholesterol

People with raised cholesterol have an increased risk of cognitive impairment and dementia in later life (112;115). This was confirmed in a recent meta-analysis (116), although in the meta-analysis the increased risk was

demonstrated for Alzheimer's dementia and overall dementia but not vascular dementia.

There is inconsistent evidence as to whether treating raised cholesterol will reduce the risk of dementia (117). Two large randomised control trials failed to show any benefit. The HPS (98) showed a reduced risk of stroke but not cognitive impairment / stroke. The Pravastatin in elderly individuals at risk of vascular disease (PROSPER) study considered 5,804 people aged 70–82 years, with a history or risk factors for vascular disease, for an average of 3.2 years follow-up. Despite a 15% relative risk reduction in a composite endpoint of vascular events there was no reduced risk of cognitive impairment (118).

However recent results from a population based cohort of 1,789 people aged over 60 followed up for 5 years indicated that the 27% of participants that took statins at any time during the study were half as likely to develop dementia (HR 0.52, 95% CI 0.34-0.8). This was after adjustment for education, smoking, diabetes and previous stroke. It may be that longer follow-up will demonstrate a benefit for statin treatment in preventing dementia but this remains to be shown in randomised controlled trials.

Diabetes

There is evidence to suggest that those with diabetes have a greater risk of developing dementia and cognitive impairment (119;120). Presently there is no evidence that tighter glycaemic control will prevent or reduce the risk of dementia in later life. However the Action to Control Cardiovascular Risk in

Diabetes - Memory in Diabetes trial (ACCORD–MIND) (121) is ongoing. The aim of this study is to test whether the rate of cognitive decline in people with diabetes treated with standard glycaemic control guidelines is different from those treated people with intensive glycaemic control guidelines.

Smoking

Studies considering smoking and risk of dementia have at times been conflicting. A recent large prospective population-based cohort study in 6,868 participants, 55 years or older and free of dementia at baseline with a mean follow-up time of 7.1 years examined this association. Current smoking at baseline was associated with an increased risk of dementia (HR 1.47, 95% CI 1.18 to 1.86) and Alzheimer's disease (HR 1.56, 95% CI 1.21 to 2.02). There was no association between current smoking and risk of vascular dementia and there was no association between past smoking and risk of dementia (122).

A meta-analysis from 2008 (123) also considered the association between current smoking and later risk of dementia. This demonstrated that smoking increases risk of developing Alzheimer' disease and suggested that it also increased the risk of overall dementia and vascular dementia, although those results were not significant.

The probable association between smoking and dementia is another reason to promote smoking cessation.

Summary

It is clear that stroke and dementia will cause an increasing health burden in the future. SES is an emerging risk factor for stroke and dementia and it is imperative that the extent and mechanism of this association is clarified. In their 2006 systematic review of SES and Stroke Cox et al (124) called for rigorous quality, prospective studies of SES and Stroke with the aim of eventually designing targeted interventions. The treatment of classical vascular risk factors has been shown to decrease the risk of stroke but the evidence that this is also the case for dementia is equivocal. Future observational studies require careful adjustment of possible confounders. Randomised control trials require longer follow-up to allow sufficient numbers of cases of dementia to accrue. Well designed studies should determine whether vascular risk factor modification is useful in preventing dementia.

This thesis aims to determine if the association between SES and stroke is due to a greater prevalence of vascular risk factors or poor oral health amongst those of low SES (Chapters 2/3/4). Chapter 4 also explores oral health after acute stroke, a previously unstudied area. Chapter 5 starts to address the common criticism of short follow-up in studies considering the association of vascular risk factors and dementia by assessing the feasibility of extending the duration of PROSPER study follow-up.

Chapter 2:

Do vascular risk factors explain the association between socioeconomic status, stroke incidence and post-stroke mortality: a meta-analysis

Introduction

Socioeconomic status (SES) is an individual's position relative to others, based on income, education and occupation. Reduced SES is associated with an increased risk of stroke (36-42). One of the most recently published large scale studies undertaken in Europe (38) considered 47,942 middle aged women and demonstrated that those in the lowest SES group were at twice the risk of stroke compared to those in the highest SES group (HR 2.1, 95% CI 1.4-2.9). There is also some evidence to suggest that those with a lower SES have increased post-stroke mortality (61-63) although other studies report no association (57;64). However it is not certain what causes the link between SES and stroke. A greater burden of vascular risk factors in lower SES groups has been shown in some studies of stroke incidence (39-41) but results are inconsistent (49).

The aim was to clarify the role of vascular risk factors in the association between stroke incidence and SES, and explore their role in a possible association between post-stroke mortality and SES. To do this a meta-analysis of all existing evidence in the area was undertaken. There was no pre-existing published meta-analysis of this important subject.

Aims

• Meta-analysis: SES and stroke incidence – the explanatory effects of vascular risk factors.

• Meta-analysis: SES and post-stroke mortality – the explanatory effects of vascular risk factors.

Methods

Review Questions

The review objectives were to perform a meta-analysis with the aim of determining whether vascular risk factors explain the association between socioeconomic status and increased stroke incidence / post-stroke mortality.

Inclusion Criteria for Studies

Studies which fulfilled the following criteria were included:

Types of study - Cohort or case-control studies.

Types of participants - Patients with a clinical diagnosis of stroke.

Types of variable - Socioeconomic status, all studies considering socioeconomic status were included regardless of choice of socioeconomic measure. Secondary variables were classical vascular risk factors. At least one classical vascular risk factor (blood pressure, smoking, diabetes, lipids, atrial fibrillation, history of vascular disease, obesity and physical activity) is examined to explain the association between socioeconomic status and stroke incidence

Types of outcome - Stroke incidence / post-stroke mortality

Search strategy for identification of studies

Articles were identified through searches of EMBASE, MEDLINE (from 1980 to September 2008) and the Cochrane Library (Issue 3, 2008) The search strategy for this review was generated following consultation with a medical librarian, consideration of relevant literature and using search terms developed by the Cochrane Stroke Group. The full search strategy is shown in Figure 2:1. The search was limited to adult populations and publications in English. The references of publication found using the above method were also searched.

Identification of relevant trials

One reviewer eliminated any obviously irrelevant or duplicate titles and then eliminated abstracts which did not obviously meet the inclusion criteria. Two independent reviewers screened all full papers. Papers were excluded if both reviewers agreed. Disagreements were resolved by discussion and, if needed, the input of a third reviewer.

Figure 2:2 describes the literature search which identified 108 full papers of which 26 were relevant to the review. Most exclusions were due to studies not considering vascular risk factors as the explanatory factor in the association between SES and stroke. Eight studies were excluded because they examined an aspect of acute stroke other than stroke incidence or mortality post-stroke. Quality of life post stroke, disability after stroke and quality of stroke care are examples of these other features of acute stroke. Eleven papers were excluded as they did not examine adult SES. Some of these considered only childhood SES but most did not examine SES at all. Six studies were excluded as they were not cohort or case-control studies (two were reviews and four were ecological studies). One study was not in English and another did not consider any aspect of acute stroke. This left 26 studies which were included in the review.

Data Extraction

Details were collected about the patients studied in each publication. This included the number in each study and any age / gender restrictions. For post-stroke mortality studies it was recorded how stroke was diagnosed, if any

patients were excluded, how long they were followed up and how mortality was established. For stroke incidence studies it was noted how stroke was diagnosed and if any patients were excluded. For all publications how SES was measured and which vascular risk factors had been adjusted for in a multivariate analysis was also documented.

In some studies several measures of SES were examined. In this case occupation was the first choice measure in the analysis; if occupation was not available income was used as the second choice. Within the same measures of socioeconomic status there were different categories. Different income brackets were used, however, in the majority of studies where occupation was examined manual versus non-manual categories were compared. In all studies the lowest socioeconomic category was compared with the highest. In Aslanyan et al (57) two SES scores were used; in this case the Murray score was used for analysis purposes as the more recently validated measure.

The least adjusted association was recorded (the association which incorporated the smallest number of covariates). For example if an unadjusted HR was available this was used but if only an age / gender adjusted HR was available this was recorded instead. For the studies looking at post-stroke mortality a univariate HR was always available. For the studies considering stroke incidence the least adjusted HR was always adjusted for age and gender (if not a single sex study) except in Xu et al (40). For this reason the age / gender adjusted HR was recorded from Xu et al to ensure consistency. The studies included in this analysis also recorded the association between SES and stroke incidence after adjustment for grouped classical vascular risk factors. The adjusted HR was also documented.

Details of included stroke incidence studies are summarised in Table 2:1. Seventeen studies considered the association between SES and stroke incidence, and also examined the effect of vascular risk factors in this association. These studies looked at stroke incidence in a total population of just over two hundred and thirty thousand. In addition 1,242 stroke patients were studied in two case control studies. However the data from five studies could not be included. Two studies (47;125) did not provide enough detail and three (54;126;127) provided adjusted but not unadjusted ratios.

Details of included post-stroke mortality studies are summarised in Table 2:2. There were nine studies that considered the association between SES and post-stroke mortality which also examined the effect of vascular risk factors on this association. Data could not be extracted from three. This was usually because not enough detail was given (58;128) but Kapral et al (61) could not be included as an adjusted HR was provided but no an unadjusted HR. The six studies included in the meta-analysis contained 8,090 patients.

The association between SES and stroke incidence or post-stroke mortality was recorded. The publications considered in this meta-analysis generally recorded this association as a HR with 95% CI, however three studies expressed the association as RR and two as an OR. Lofmark et al (129) analysed their data in two groups, patients who were aged under 75 and those 75 or over. For the purposes of this analysis the under 75 group was used. Avendeno et al (130) analysed their data in three groups, patients aged 55-64, 65-74 and 75+. For the purposes of this analysis the aged 55-64 group was used.

Data Analysis

Statistical pooling of the unmodified and modified HR (95% CI) of socioeconomic status and stroke incidence / post-stroke mortality was performed to generate a graphical display of comparable results. This pooling was done using a random effects model as substantial heterogeneity was expected. In each analysis the degree of heterogeneity was calculated. This provided a summary result (with 95% CI) for all available studies, weighted by study size. All analysis was undertaken using the Cochrane collaboration's review manager statistical software package, Review Manager 5 (RevMan. Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

Figure 2:1 Meta-analysis Search Strategy

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or cerebrovascular accident/ or exp brain infarction/ or exp cerebrovascular trauma/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or intracranial arteriovenous malformations/ or exp "Intracranial Embolism and Thrombosis"/ or exp intracranial haemorrhages/ or vasospasm, intracranial/ or vertebral artery dissection/

2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.

3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

5. 1 or 2 or 3 or 4

6. exp Socioeconomic Factors/ or exp Social Class/ or exp Income/ or exp Education/ or exp Poverty

7. (social$ or socio$) adj3 (inequalit$ or depriv$ or class$ or status or factor$).tw.

8. socioeconomic.tw.

9. 6 or 7 or 8

17. 5 and 9

The search strategy was modified to suit different databases

Figure 2:2 Meta-analysis Search Flow

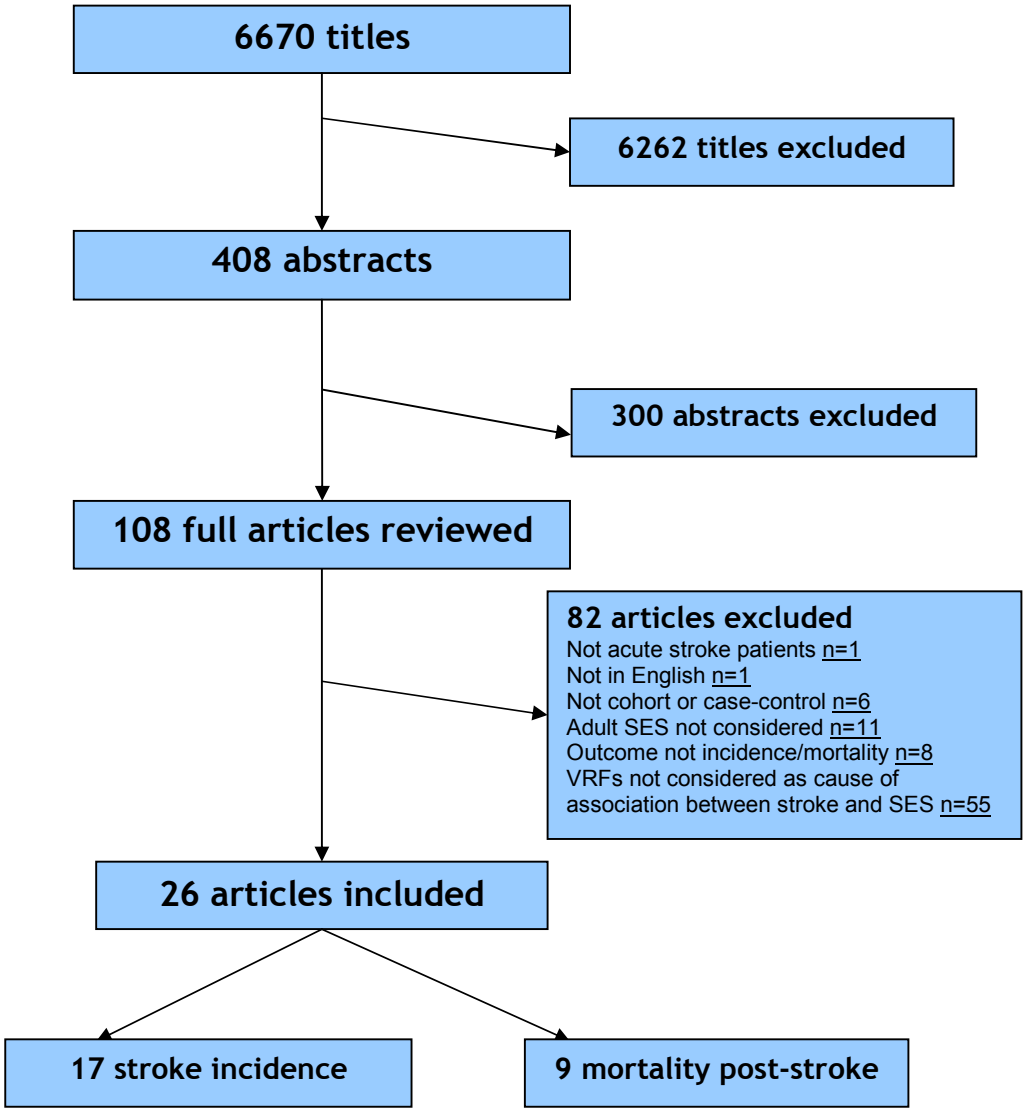


Table 2:1 Studies evaluating role of vascular risk factors in association between socioeconomic status and acute stroke incidence

Author	Patient group	How was stroke diagnosed?	Endpoint	How is socioeconomic status measured?	Grouped vascular risk factors adjusted for (other non vascular factors in group)*	Data available and extractable
Avendano 2006 (41)	2,812 age 65+ adults in Connecticut, USA	Self reporting (patient or family), or obituaries / hospital records if fatal	Non-fatal or fatal stroke	Income, Education	Hypertension, Diabetes, Smoking, Alcohol, Exercise, Obesity, (Race)	Yes (HR)
Avendano 2008 (130)	19,565 age 50+ adults in USA	Self reporting (patient or proxy) {TIA excluded}	Non-fatal or fatal stroke	Income, Education, Wealth,	Hypertension, Diabetes, Smoking, History of IHD, Exercise, Obesity (Race, Childhood illness)	Yes (HR)
Brown 2005 (125)	1,242 stroke patients in Auckland with 2247 controls	Clinical and from death certificates	SES as predictor of stroke	Income, Household income	Hypertension, Diabetes, Smoking, Alcohol, Obesity (Race)	No
Gillum 2002 (44)	5,614 age 25-74 in USA	Death certificates and hospital discharge	Non-fatal or fatal stroke	Education, Poverty index	Blood Pressure, Diabetes, Smoking, History of heart disease, Alcohol, Physical activity	Yes (RR)
Goldbourt 2007 (54)	10,000 men aged 40 to 65 in Israel	Mortality registry	Fatal stroke	SES Scale (based on Salary / Education)	Blood Pressure, Diabetes, Smoking, Obesity	No
Hart 2000(Mar) (37)	5,765 men aged 35-64 in Scotland	Hospital discharge / Death registry coding	Non-fatal or fatal stroke	Occupation, Father's occupation, Carstairs & Morris deprivation category	Blood Pressure, Smoking, History of IHD, Alcohol (Height, FEV1)	Yes (HR)
Hart 2000(Nov) (46)	14,947 age 45-64 in Scotland	Hospital discharge / death registry coding	Non-fatal or fatal stroke	Occupation, Carstairs & Morris deprivation category	Blood Pressure, Smoking, Lipids, History of IHD, Alcohol, BMI (Height, FEV1)	Yes (HR)
Kuper 2006 (38)	47,259 women aged 30-49 in Sweden	Hospital discharge / Death registry coding	Non-fatal or fatal stroke	Education	Hypertension, Diabetes, Smoking, Obesity, Alcohol, Exercise	Yes (HR)
Laaksonen 2007 (53)	60,518 aged 25-64 in Finland	Death registry coding	Fatal stroke	Education	Smoking, Alcohol, Relative weight, Physical activity (Vegetable use, Fat on bread, Coffee drinking)	Yes (HR)
McCarron 2001 (39)	4,861 men in Caerphilly / Bristol	Self reporting (with hospital / GP notes) & death registry	Non-fatal or fatal stroke	Occupation	Blood Pressure, Diabetes, Lipids, Smoking, History of IHD, Atrial Fibrillation	Yes (HR)

Table 2:1 cont.

Author	Patient group	How was stroke diagnosed?	Endpoint	How is socioeconomic status measured?	Grouped vascular risk factors adjusted for (other non vascular factors in group)*	Data available and extractable
Metcalfe 2005 (68)	5,577 men aged 35-64 in Scotland	Hospital discharge / death registry coding	Non-fatal or Fatal stroke	Occupation, Father's occupation	Blood Pressure, Lipids, Smoking , Alcohol, Obesity, Exercise (FEV1)	Yes (HR)
Peltonen 1999 (47)	4,215 first stroke patients aged 25-74 in northern Sweden	Stroke registry / Death registry coding	Non-fatal or fatal stroke	Occupation	Diabetes, Atrial Fibrillation	No
Power 2005 (36)	11,855 women aged 14-49 in UK	Death registry coding	Fatal stroke	Husband's occupation / Father's occupation	Smoking, BMI	Yes (HR)
Salonen 1982 (126)	3,644 men aged 30-59 in Finland	Hospital discharge / Death registry coding	Non-fatal or fatal stroke	Income, Education, Episodes of unemployment, Residence	Blood Pressure, Lipids, Smoking	No
Van Rossum 1998 (49)	4,274 women 55+ in Netherlands	Self reporting (medical records) & GP records	Non-fatal or fatal stroke	Occupation, Education, Household Income	Blood Pressure, Hypretension, Diabetes, Smokng, Obesity, Alcohol, History of IHD, Atrial Fibrillation, Left ventricular hypertrophy, (Fibrinogen)	Yes (RR)
Vitullo 1996 (127)	237 patients aged 30-69 with ischaemic stroke and 928 controls	Clinical	SES as predictor of stroke	Occupation, Education	Blood Pressure, Diabetes, Lipids, Smoking, Obesity, Alcohol, Exercise	No
Xu 2008 (40)	29,340 aged 35+ in China	Self-reporting	Stroke	Occupation, Family average income, Education	Hypertension, Diabetes, Smoking, Obesity, Alcohol, Physical activity	Yes (HR)

Also adjusted for Age and Gender (or if single sex study adjusted for Age)

Table 2:2 Studies evaluating role of vascular risk factors in association between socioeconomic status and post-stroke mortality

Author	Patient group	How was stroke diagnosed?	Follow-up (source of Information)	How is socioeconomic status measured?	Grouped vascular risk factors adjusted for (other non vascular factors in group)*	Data available and extractable
Arrich 2004 (56)	2,606 post stroke patients in Vienna, Austria (Haemorrhage excluded)	Clinical including imaging	2.5 years (Mortality database)	Occupation, Education, Occupational status, Income	Hypertension, Elevated lipids, Diabetes, Smoking, History of stroke, History of IHD, History of PVD	Yes (HR)
Aslanyan 2003 (57)	2,026 post first stroke patients 18+ in Glasgow, Scotland (Haemorrhage excluded)	Clinical including imaging	Minimum of 2 years (Death registry)	Murray & Wormsley deprivation scores	Hypertension, Elevated lipids, Diabetes, Atrial Fibrillation, History of stroke or TIA, History of IHD, History of PVD, Family history of stroke, Alcohol use	Yes (HR)
Kapral 2001 (61)	38,495 post stroke aged 20-105 in Ontario, Canada	Hospital discharge coding	30 days and 1 year (Death registry)	Neighbourhood Mean income	Hypertension, Diabetes, Atrial Fibrillation, History of IHD and CCF, History of PVD, Obesity † (Chronic lung disease, Charlson co-morbidity score)	No
Lofmark 2008 (129)	610 post stroke aged 20-85 in Umea, Sweden	Hospital discharge coding / Stroke registers	28 days (Hospital discharge coding / Stroke registers / Death registry)	Education	Diabetes, Atrial Fibrillation, History of stroke, History of IHD, Ischaemic ECG	Yes (OR)
Ngeh 2007 (128)	100 cases of TIA or Stroke in elderly patients with 87 controls in London, England	Clinical	6 years (Health records)	Index of multiple deprivation, Income depriivation affecting older people index	Hypertension, Diabetes, Smoking, History of IHD, Ischaemic ECG †	No
Samanci 2004 (63)	147 post first stroke patients aged 18+ (TIA, SAH, Bilateral stroke, Cerebellar stroke or previously dependent excluded	Clinical	1 year	Occupation, Education	Elevated lipids, Smoking, History of IHD, (Marital status, Medical health insurance, Urinary incontinence) ‡	Yes (OR)
Weir 2004 (58)	2,709 post stroke patients in Scotland	Hospital discharge	6 months (Death certificate)	Carstairs and Morris deprivation category (based on occupation)	Diabetes, History of IHD ,History of stroke, High Blood Pressure at admission (Premorbid ADL, Lived alone, Urinary Incontinence)	No
Wong 2006 (64)	2,042 post stroke patients in Dundee, Scotland	Clinical	1 year (Death register)	Carstairs and Morris deprivation category (based on occupation)	Atrial Fibrillation, Abnormal ECG {ischaemia, LVH or heart block}, Blood glucose, (Premorbid IADL)	Yes (RR)
Zhou 2006 (62)	806 first ischaemic stroke patients in China (SAH, Haemorrhage excluded)	Stroke registry based on WHO clinical criteria	3 years	Occupation, Education, Income, Housing Space	Hypertension, Elevated lipids, Diabetes, Smoking, , Atrial Fibrillation, History of TIA, History of MI	Yes (HR)

* Also adjusted for Age, Gender and Stroke Severity

† Kapral / Ngeh did not adjust for Stroke Severity

‡ Samanci did not adjust for gender

Results

Stroke Incidence

Figure 2:3 is a Forrest Plot and summarises the unadjusted risk (shown as HR) of stroke incidence in the lowest SES group compared to the highest SES group. Each individual study's HR (95% CI) is seen with overall HR shown on the last line of the plot. This demonstrates that compared to those in the highest SES group those in the lowest group had a greater risk of stroke (HR 1.67; 95% CI 1.46-1.91).

Figure 2:4 summarises the adjusted risk of stroke incidence in the lowest SES group compared to the highest SES group. This is the risk adjusted for grouped vascular risk factors; these grouped vascular risk factors differed between studies but shared similar components. These are detailed in column 6 of Table 2:1. When the risk is adjusted for grouped vascular risk factors it reduces (HR 1.31; 95% CI 1.16-1.48) but is not abolished.

Figure 2:5 shows a graphical representation of the increased risk of stroke incidence in those with lower SES and how the risk reduces when vascular risk factors are adjusted for. Each study is shown individually. Only Van Rossum et al (49) did not show a reduction in HR when grouped vascular risk factors were adjusted for.

Three studies (44;46;53) examined the results for men and women separately and these separate results are shown on Figures 2:3, 2:4 and 2:5.

Post-stroke Mortality

Figure 2:6 summarises the unadjusted risk (shown as HR) of post-stroke mortality in the lowest SES group compared to the highest SES group. Each individual study's HR (95% CI) is seen with overall HR shown on the last line of the plot. This demonstrates that compared to those in the highest SES group those in the lowest group were more likely to die after their stroke (HR 1.48; 95% CI 1.07-2.05). Stratification for length of follow-up suggested a tendency for increased risk post-stroke mortality for those in lowest SES group in studies where follow up was ≤ 1 year (HR 1.83: 95% CI 0.98-3.39), but this was not significant as the 95% confidence interval just passes through 1.0. There was no significant association in studies where the follow-up was >1 year (HR 1.39; 95% CI 0.65-2.99).

Figure 2:7 summarises the adjusted risk of post-stroke mortality in the lowest SES group compared to the highest SES group. This is the risk adjusted for grouped vascular risk factors; these grouped vascular risk factors differed between studies but shared similar components. These are detailed in column 6 of Table 2:2. When the risk is adjusted for grouped vascular risk factors there is no significant change in risk (HR 1.75; 95% CI 1.16-2.65). However these results showed significant heterogeneity (I^2 88% / 87%).

Figure 2:3 Risk of incident stroke onset risk in the lowest versus highest socioeconomic group

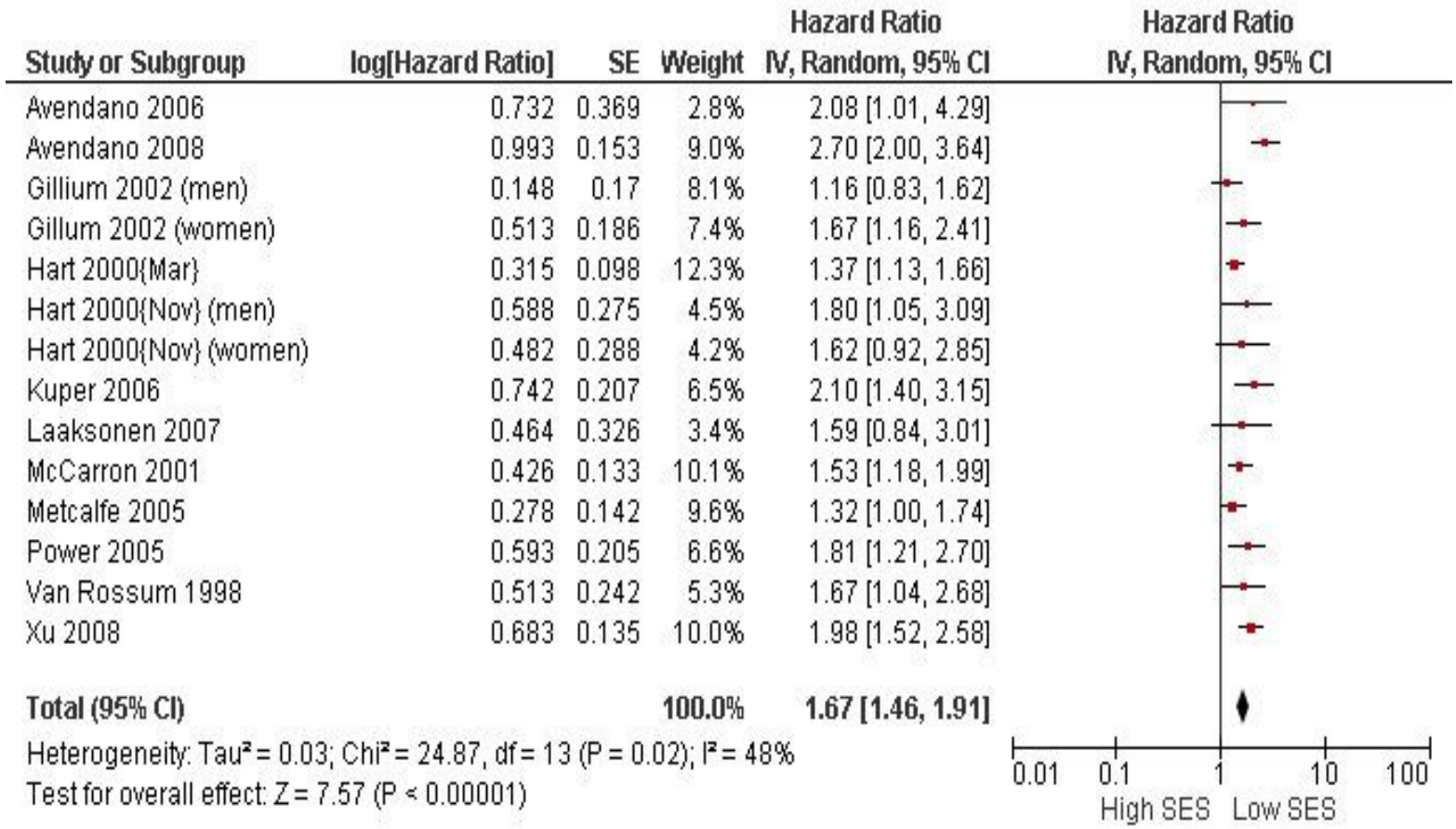


Figure 2:4 Risk of incident stroke onset in the lowest versus highest socioeconomic group adjusted for grouped vascular risk factors

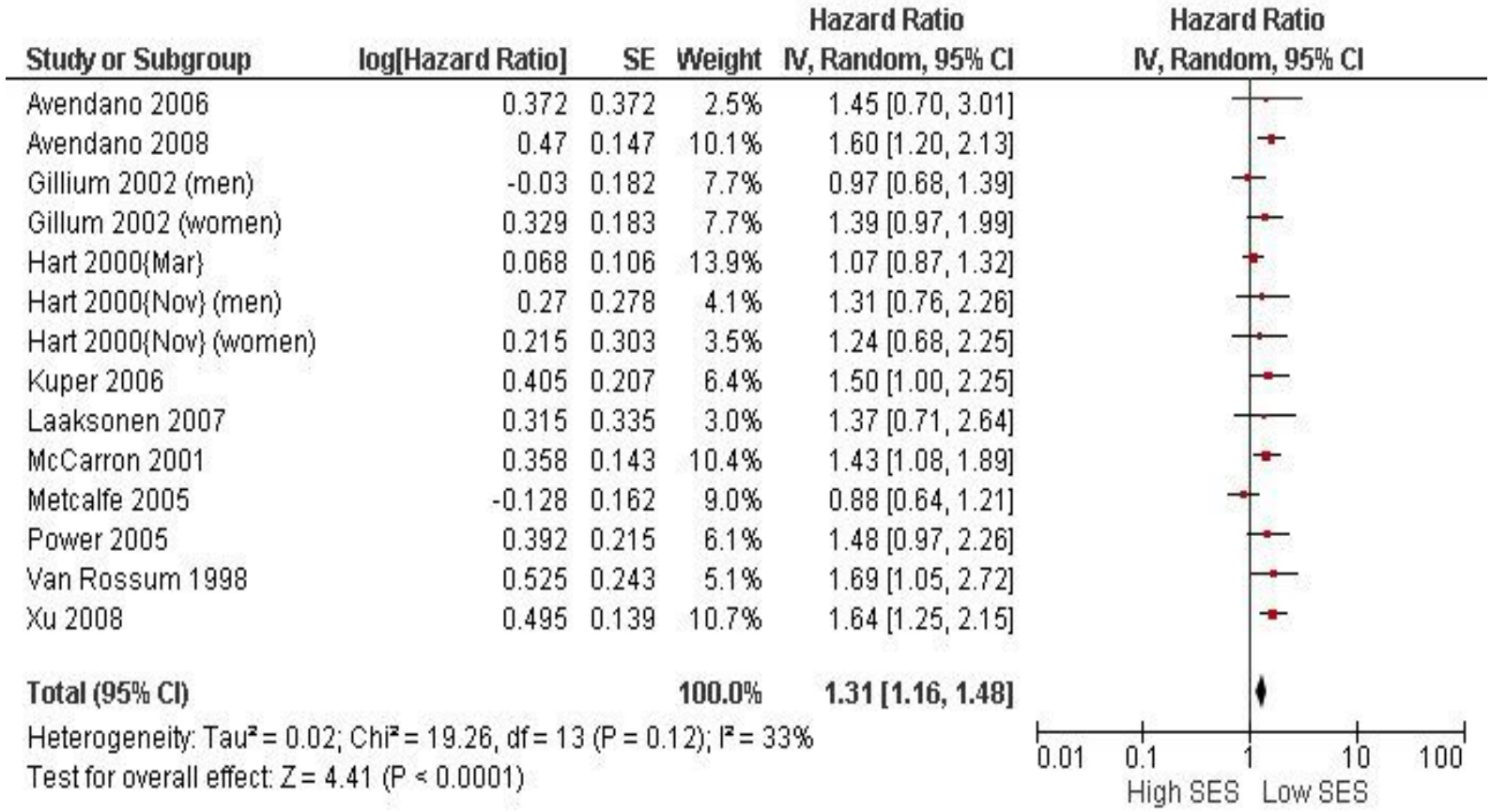


Figure 2:5 Graphical representation of the risk of stroke incidence in the lowest versus highest socioeconomic group – unmodified versus modified for grouped vascular risk factors

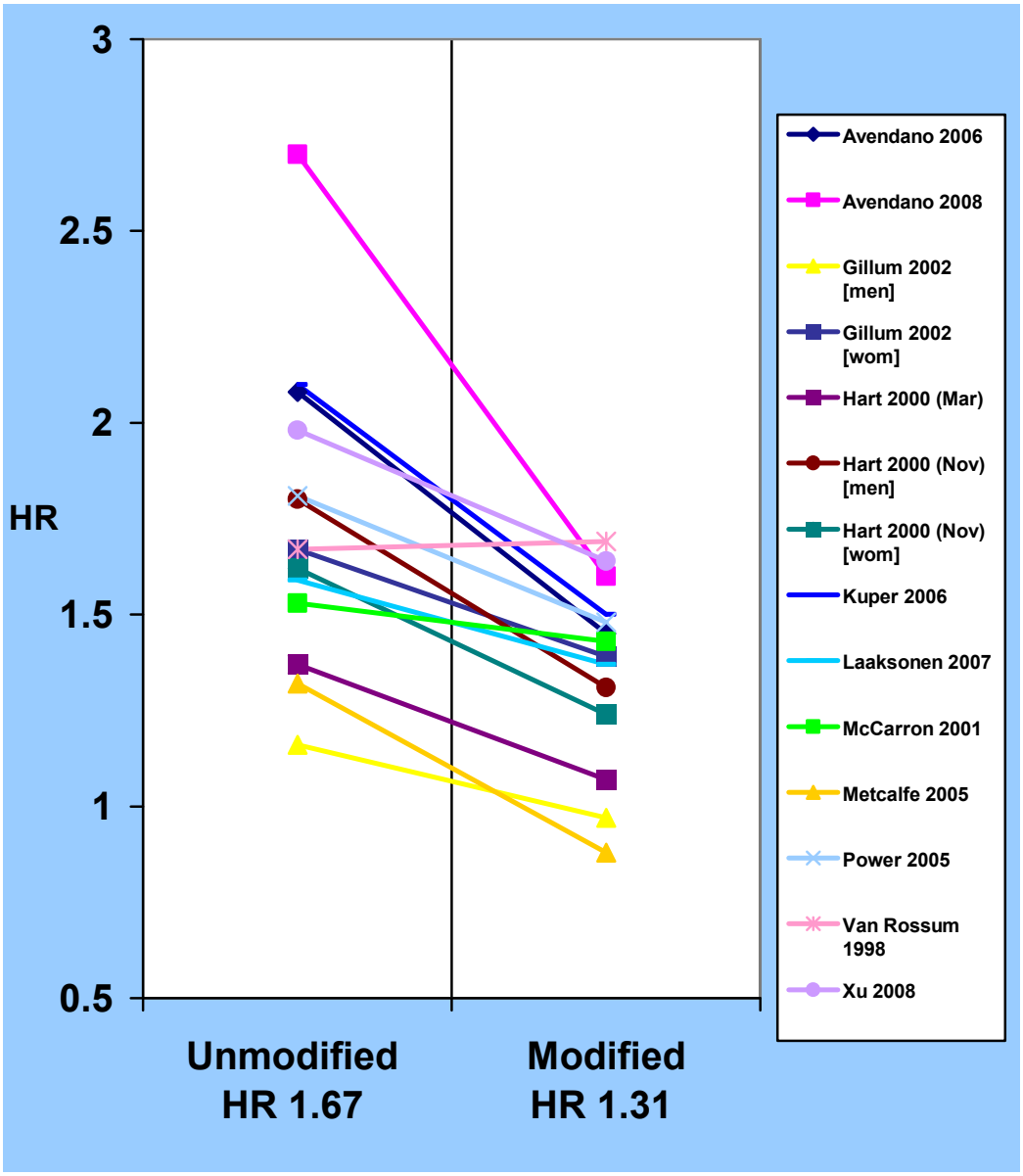


Figure 2:6 The risk of post-stroke mortality in the lowest versus highest socioeconomic group (shown in two sub-groups, follow-up of 1 year or less and follow-up of more than 1 year)

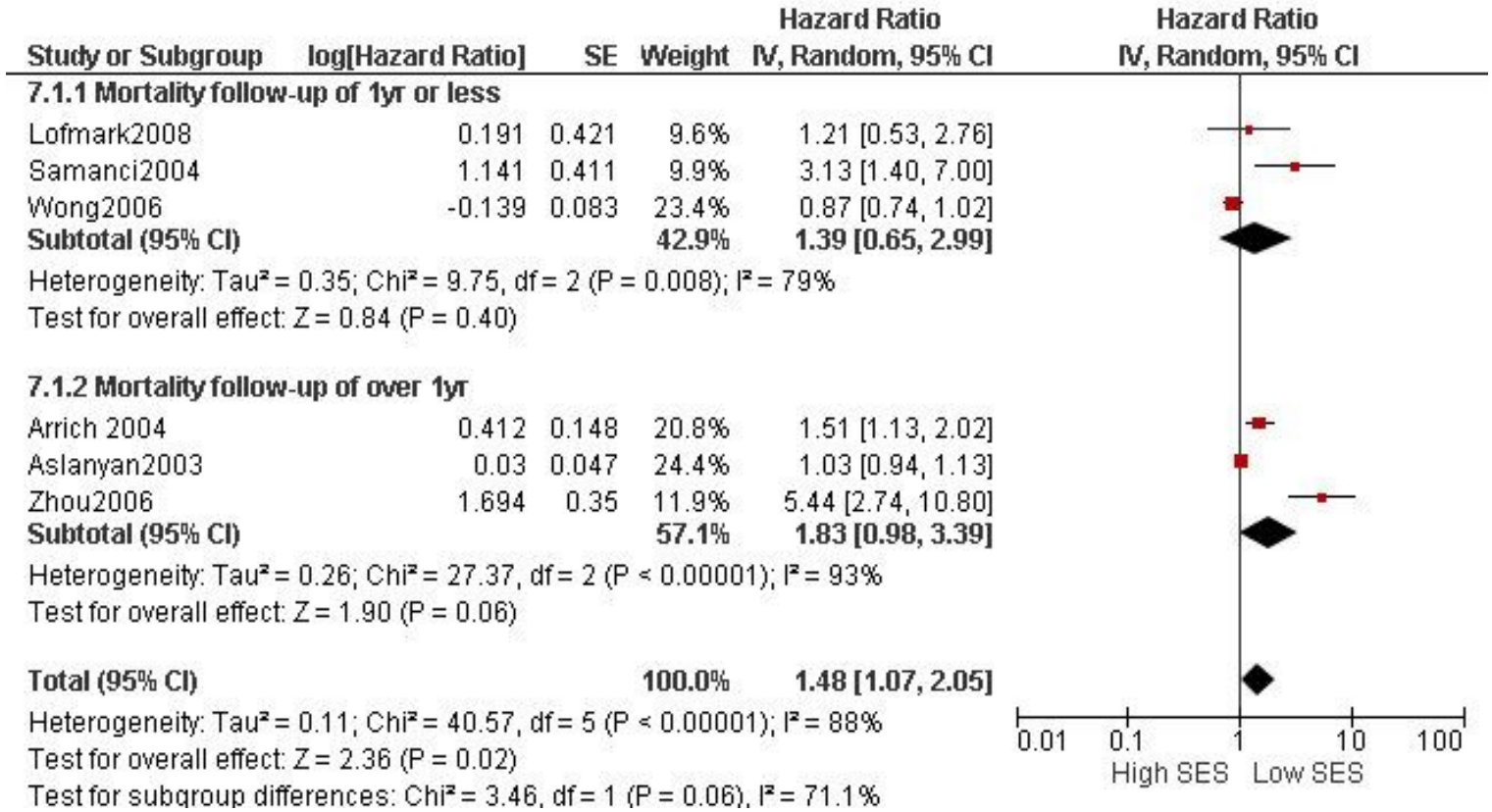
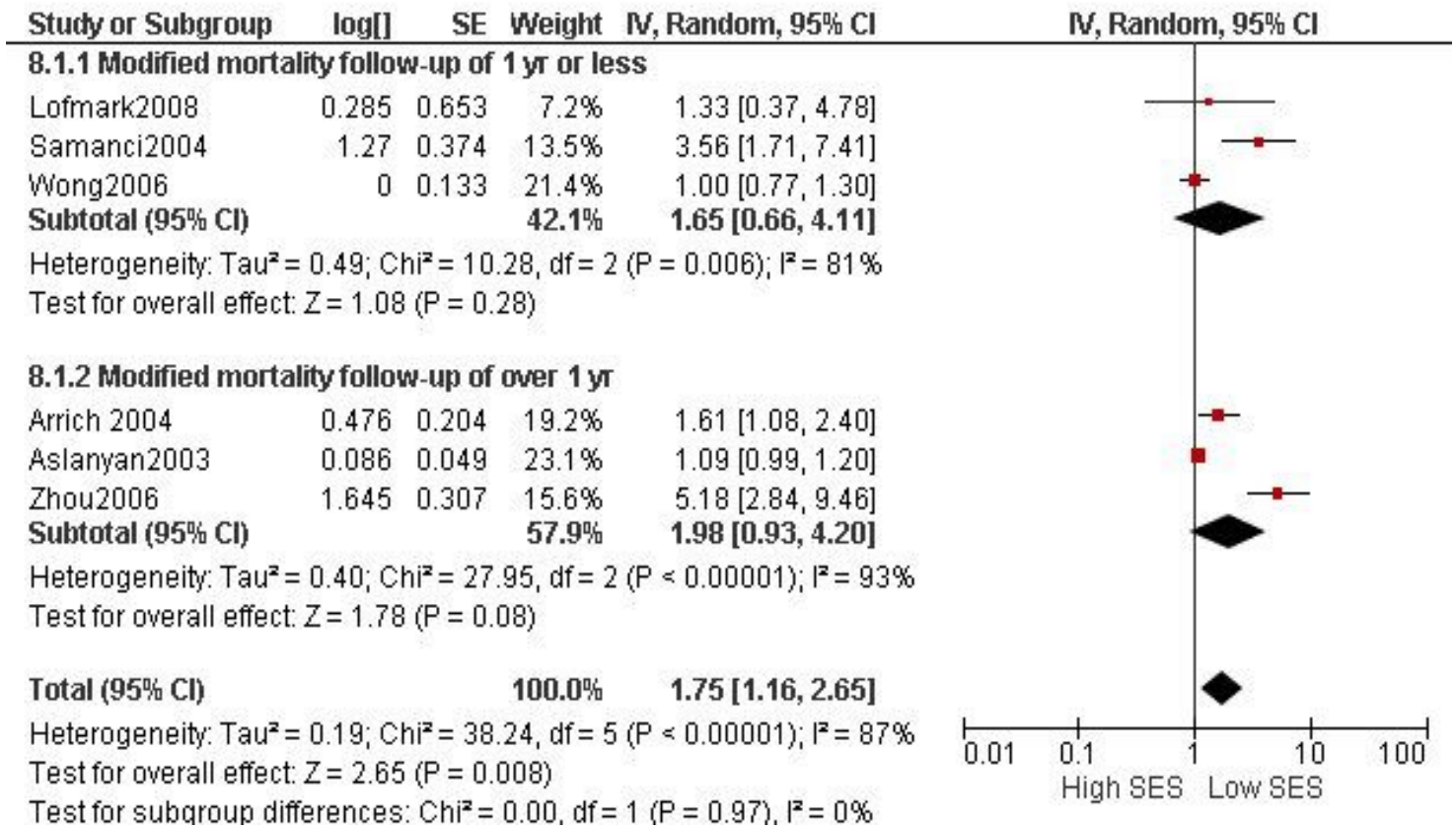


Figure 2:7 The risk of post-stroke mortality in the lowest versus highest socioeconomic adjusted for grouped vascular risk factors (shown in two sub-groups, follow-up of 1 year or less and follow-up of more than 1 year)



Discussion

This meta-analysis found that grouped classical vascular risk factors explain some, but not all, of the increased risk of stroke amongst those with a reduced socioeconomic status. There is evidence of a greater burden of vascular risk factors amongst those from lower SES groups (39-41) but we are able to provide an overall estimate of how much this burden may explain the association between stroke and SES. After adjustment for vascular risk factors the risk was reduced from HR 1.67 (95% CI 1.46-1.91) to HR 1.31 (95% CI 1.16-1.48), roughly a 50% decrease in additional risk. It is likely that the association between stroke risk and SES is multifactorial.

The results of this meta-analysis indicate that grouped vascular risk factors do not significantly attenuate the increased risk of post-stroke mortality amongst the lower SES groups. Therefore these results suggest that the higher post-stroke mortality seen in association with lower SES is not due to greater burden of vascular risk factors. However there is significant heterogeneity between the results of the six studies in this part of the meta-analysis with two of the six studies not showing an increased risk of post-stroke mortality in the lower SES group. The design of the studies also varied substantially. Duration of follow-up ranged between 28 days and 6 years, different measures of SES were used and the grouped vascular risk factors differed although they share similar components. Therefore the conclusions drawn from the post-stroke mortality meta-analysis should be interpreted with caution because of heterogeneity and the small number of studies involved.

There is some evidence that those in lower SES groups have reduced access to stroke care (45) and it is possible that even when available those in low SES groups make less use of stroke services. Additionally there is also evidence that the early life influences of those with low SES, such as poor maternal nutrition leading to low birth weight and subsequent vascular disease (74), may explain some of the association between SES and stroke incidence. Other factors such as reduced exercise, poor diet and novel vascular risk factors such as C-reactive protein may play a part in the association between low SES and increased stroke incidence. Therefore the association between socioeconomic status and stroke is likely to be multifctorial but we believe that vascular risk factors are likely to be an important component of this association and public health care messages regarding these should be targeted at low SES groups.

It was beyond the scope of the stroke incidence meta-analysis to establish which specific vascular risk factor was most important. The vascular risk factor groups used in each study varied although they shared many similar components. All included smoking and all but two included blood pressure (36;53). There is growing evidence that smoking may be the most consistent vascular risk factor in the association of SES and stroke (38;46;130) and it is interesting to note that it was the one risk factor common to all 12 studies used in this meta-analysis. Further research is needed to establish which vascular risk factor is most critical when considering SES and stroke. In addition future research should also consider novel and emerging vascular risk factors such as C-reactive protein.

Strengths and Weaknesses

The main strength of this meta-analysis is that a rigorous systematic review approach has been used (131) and a large number of acute stroke patients were included. There has not been a meta-analysis in this area before. In addition the included stroke incidence studies showed a reasonable consistency of both unadjusted and adjusted results. All studies, other than van Rossum et al (49), showed a reduction in risk after adjustment for vascular risk factors. This consistency is reassuring and is despite the heterogeneous nature of the studies included. Van Rossum et al may have failed to show an affect as they lacked the extremes of SES and had only a narrow mid-range of SES. They also had a short follow-up.

The main weakness of this review was the heterogeneity of the studies. This includes the varying measure of SES and the different grouping of vascular risk factors, some of which included non vascular risk factors. Most studies used occupation to measure SES but two studies used income (41;130) and three used education (38;44;53). In addition the age group of study participants varied and some studies examined only one gender. Lastly three studies (36;53;54) looked at the incidence of fatal stroke only.

Another weakness is that not all studies described the association of SES and stroke incidence / post-stroke mortality using hazard ratios. Five of the eighteen studies used in the meta-analysis did not use hazard ratios. Three studies (44;49;64) used relative risk and two studies (63;129) used odds ratio. These different measures of risk were combined and we are aware this could be

criticised. Finally it is not possible to decipher which vascular risk factor may be critical in explaining the association between SES and stroke incidence.

Summary

In summary, this meta-analysis shows that lower SES is associated with an increased risk of stroke. This is partly explained by known classical vascular risk factors. Low SES is also associated with increased mortality risk in those who have a stroke; this link is not readily explained by known vascular risk factors.

Smoking cessation, control of blood pressure and management of other vascular risk factors should be made a priority in areas of low SES. Additionally, further research is needed to fully clarify the association between SES and stroke incidence. Avenues for exploration might include the possibilities of poorer access to effective stroke care or reduced uptake of preventative treatments in lower socioeconomic groups.

Chapter 3:

Socioeconomic status and transient ischaemic attack / stroke: a prospective observational study

Introduction

Socioeconomic status (SES) is an individual's position relative to others, based on income, education and occupation. Low SES is associated with an increased risk of stroke (36-40;42;130) and those who are from lower socioeconomic groups may have more severe neurological impairment (57;58). However it has never been fully established what causes the link between low SES and stroke. A greater burden of vascular risk factors in lower SES groups has been shown in some studies (39;40;130) but results are inconsistent (49). It is possible that low SES patients may not have equitable access to health care (45).

The aim was to determine whether TIA and stroke patients with low SES have greater burden of vascular risk factors and co-morbidity compared to those from a more affluent background. Additionally to examine whether low SES is associated with reduced access to and utilisation of health care. This was done by studying a prospective, consecutive cohort of both inpatient and outpatient TIA and stroke patients. Previous studies in this area have rarely considered outpatients and are often retrospective. There is also little pre-existing evidence on the role of health care utilisation in the association between TIA / stroke and SES. This study was undertaken in the West of Scotland, where there is a high rate of stroke disease but free health care is provided to the whole population as part of the nationalised health service.

Aims

• To characterise the frequency of vascular risk factors (blood pressure, cholesterol, diabetes, cigarette smoking) in TIA / stroke patients and too assess whether those patients with low SES carry higher levels of vascular risk factors.

• To determine the frequency of pre-existing vascular disease in TIA / stroke patients and too assess whether those patients with low SES carry higher levels of pre-existing vascular disease.

• To establish whether TIA / stroke patients from different SES groups have equal access to stroke care services and investigations.

• To assess whether those patients from lower SES groups have a more severe TIA / stroke.

Methods

Anonymised data was abstracted on 467 consecutive TIA and stroke patients referred to 3 acute hospitals in the West of Scotland; at Glasgow Royal Infirmary between November 2007 and April 2008, and at the Western Infirmary, Glasgow and Ayr Hospital during May and June 2008. These comprise urban (Royal and Western Infirmaries) and mixed rural / urban (Ayr Hospital) catchments. The diagnosis of TIA or stroke was made by a stroke physician working to the World Health Organisation (WHO) diagnostic criteria (1) and confirmed, where appropriate, with neuroimaging. Both inpatients and outpatients with a

specialist clinical diagnosis of TIA or Stroke were included. The only exclusion criterion was a diagnosis other than TIA or stroke. In addition all new patients referred for outpatients assessment who did not attend their appointment had their referral information reviewed by two stroke physicians and a judgment made as to whether a recent TIA or stroke was likely.

To ensure all consecutive inppatients were included there was daily checking at each of the three hospitals stroke units, acute receiving units and accident and emergency departments. This included verification of patients with stroke who had died before reaching the stroke units. Referrals to the stroke team from other areas of the hospital were reviewed and there was also a regular check on all other wards.

Data which were already collected as part of routine clinical care was collated from patient case notes. Initial information was recorded as soon after admission or outpatient review as possible and the data was collected by the same investigator at each of the three sites. SES was derived from post codes using Scottish Neighbourhood Statistics (28). This is a Scottish government programme using information on education, employment, environment, health, housing, crime & access to services to generate small area statistics on SES. It provides an index of SES for each Scottish post code from 1 (lowest SES) to 6505 (highest SES) and this index is known as the Scottish Index of Multiple Deprivation. The patient's post code was recorded and then a Scottish Neighbourhood index generated for each of the patients in this study. About a thousand people live in each of these post code areas. The SES index range in this study was 8-6445 with a mean of 1876. The patients were analysed in quartiles, the lowest quartile had

a SES index ranging from 8-379, second quartile 380-1132, third quartile 1133-2927 and highest quartile 2927-6445.

Demographic information was collected and included age and gender. Where in the hospital the patient was treated, how quickly they arrived and whether they had thrombolysis was also recorded. Past medical history was reviewed and a history of hypertension, raised lipids, diabetes, ischaemic vascular disease (cerebrovascular disease, IHD and peripheral vascular disease) and revscularistation noted. Previous revascularisation was defined as a history of coronary artery bypass graft, coronary angioplasty, carotid endarterectomy or femoral-popliteal bypass or angioplasty. Past medical history also allowed the calculation of the modified Charlson Index. This measure has been validated for use in stroke patients (132) but this co-morbidity index was originally developed in 1987 based on 1-year mortality data from internal medicine patients admitted to a New York Hospital and was initially validated within a cohort of breast cancer patients. The index originally encompassed 19 medical conditions weighted 1–6 with total scores ranging from 0–37 (133).

Data on admission blood pressure (BP), total cholesterol, high density lipoprotein (HDL) cholesterol, blood glucose, cigarette smoking status, family history of IHD or TIA / stroke and medication was also collected. The admission modified National Institute of Health Stroke Score (mNIHSS) (134) was determined; this has been validated as a means of calculating stroke severity from case notes (135). The Oxfordshire Community Stroke Project (OCSP) (136) stroke subtype was also recorded.

The patient case notes were reviewed throughout the admission and at discharge, allowing investigation results to be recorded. Investigations recorded

were 12 lead electrocardiogram (ECG), computerised tomography (CT) or magnetic resonance imaging (MRI) brain scan, echocardiogram and carotid imaging. For outpatients and those inpatients who had some or all of their investigations after discharge, a regular check up of radiology and cardiology results was undertaken and if necessary hospital records were reviewed again.

Additionally it was thought that the admission blood pressure would not necessarily reflect the usual blood pressure of the patients and a later blood pressure was also recorded. This was either the blood pressure one week after admission, or if antihypertensives were started or restarted prior to one week after admission, then the blood pressure immediately before this was done. If patients were discharged less than a week after admission their blood pressure at discharge was considered to be their later blood pressure. For outpatients their admission blood pressure was the blood pressure recorded by their General Practitioner or Accident and Emergency staff and the later blood pressure was the blood pressure recorded in the outpatient clinic.

The Multi-Centre Research Ethics Committee of Scotland advised that, as the data gathered in this study was collected as part of routine clinical care, a formal ethics submission for use of anonymised data was not necessary.

Statistical Analysis

Indicative power calculations were performed. We determined for an α of 5% (2-tailed) and a 1-β of 80%, assuming a smoking rate of 45% or prevalence of hypertension of 50%, that a minimum of 460 total patients would be required to

detect a difference of 13% between the lowest quartile of socioeconomic status and other patients. Assuming a standard deviation for systolic blood pressure of 20 mmHg, 502 total patients would be needed to detect a difference of 5 mmHg. Our aim was therefore to study 502 patients, with a minimum target of 460. The assumption for prevalence of risk factors was based on several previous acute stroke studies, two of which were also conducted in Glasgow (57;137;138). These calculations were based on the formula suggested by Campbell et al (139).

SES was categorised in quartiles for the purpose of statistical analysis. Univariate analysis was undertaken using Analysis of Variance for normally distributed continuous variables, Kruskal-Wallis H test for non-normally distributed continuous variables and the Chi-squared test for categorical variables. To assess normality the Skewness and Kurtosis statistics was used. Results of continuous variables are given as mean (standard deviation (SD)), categorical variables given as number (%) and non-normally distributed variable results are shown as median (IQR).

To examine the independent associates of key vascular risk factors, such as smoking and stroke severity, regression analysis was performed. Where the dependent was binary, such as smoking, binary logistic regression was performed. When the dependent was a continuous variable linear regression analysis was performed. This was done using the enter method with entry at p=0.05 and removal at 0.10.

All analyses were performed using SPSS for Windows version 15.0

Results

Patient characteristics are described in column 1 of Table 1. There were 467 patients with an average age of 68.6 (SD 14.1). Two hundred and thirty five (50.3%) were women and 145 (31.3%) had a TIA.

SES was generated for 464 of 467 consecutive TIA and stroke patients. This could not be calculated for three patients, two were from outwith Scotland and the post code of one patient was not available. Figure 3:1 shows the frequency of SES score. Just over a third of the cohort were in the lowest 10% of Scottish SES (cut off score <650). This reflects the fact that the West of Scotland has, in general, a lower socioeconomic profile compared to Scotland as a whole.

Vascular Risk Factors

A univariate analysis of SES and traditional vascular risk factors, past medical history of vascular disease, chronic disease and co-morbidity is shown in Table 3:1. Overall 17.1% of TIA and stroke patient had diabetes, 54.4% had a history of hypertension and 52.9% had a history of raised lipids. In addition 32.8% of the TIA and stroke patients were current smokers and 11.6% had a family history of IHD or cerebrovascular disease in a first-degree relative ≤60 years. The mean admission systolic / diastolic BP was 148 (27)/82 (18) mmHg and the later blood pressure was 136 (SD 22)/76 (SD 13) mmHg. Mean admission total cholesterol was 4.6 (SD 1.3) mmol, HDL cholesterol 1.2 (IQR 0.9-1.5) mmol and median glucose 6 (IQR 5.3-7.1) mmol/L.

Stroke and TIA patients in the lowest socioeconomic quartile were younger (63.9 [SD 14.1]) compared to those in the highest quartile (72.1 [12.9], p<0.0001). More were current smokers (42.4% versus 21.6%, p=0.001). Stroke and TIA patients in the highest SES quartile more frequently had a history of ischaemic vascular disease (56.9% versus 44.1%, p=0.03) and previous revascularisation (13.8% versus 4.2%, p=0.018). There was also a tendency for those in the highest SES quartile to have a history of hypertension although this did not reach statistical significance (55.2% versus 44.3%, p=0.059). There was no difference by SES in prior active management of known ischaemic vascular disease with antithrombotics or statins. There was no association of SES with other vascular risk factors, past medical history or co-morbidity on univariate analysis.

To examine whether current smoking is independently associated with SES a binary logistic regression analysis was performed with current smoking as the dependent (Table 3:2) and independent variables; gender, age, quartiles of SES and history of ischaemic vascular disease (ischaemic heart disease, previous cerebrovascular disease or peripheral vascular disease). After adjustment for these other factors SES associated independently with smoking in this group of TIA and stroke patients (beta=0.191, p=0.046).

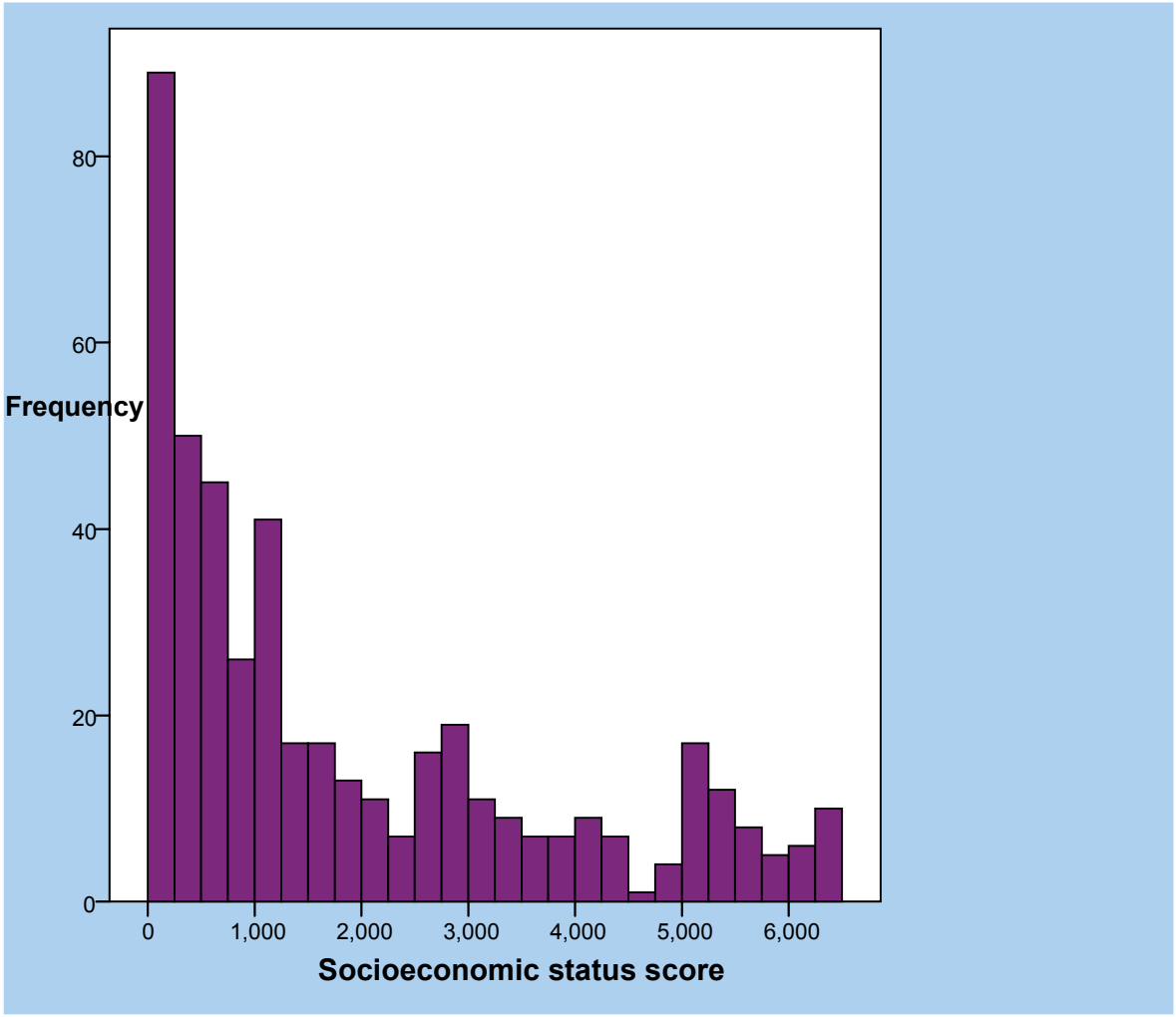
Linear regression analysis with diastolic BP as the dependent (Table 3:3) and independent variables; gender, age, quartiles of socioeconomic status and stroke severity (mNIHSS), showed socioeconomic status was independently associated with admission diastolic BP (beta=0.125, t=2.415, p=0.016), with those with a lower SES more likely to have a lower admission diastolic BP.

Multivariate analyses examining whether hypertension, revascularisation or prior known ischaemic vascular disease (dependent variables) were independent

associates of SES were undertaken (Tables 3:4, 3:5 and 3:6). The independent variables in these analyses were gender, age, SES and smoking. The apparent association of hypertension with higher SES in univariate analysis was no longer present when corrected for the above factors; increased age was the only variable associated independently with history of hypertension. Higher SES was not independently associated with history of ischaemic vascular disease when corrected for age, gender and current smoking. There was a trend for history of revascularisation to be independently associated with higher SES although this was not statistically significant (beta=0.312, p=0.054).

A sub-group analyses of TIA and stroke patients separately showed few apparent important differences in terms of SES and vascular risk factors, severity or health care utilisation, but there was an association with SES and family history of IHD / TIA / stroke for those in the stroke sub-group. Those in the upper quartile of SES were more likely to have a family history of IHD / stroke (40%) than those in the lowest quartile (16.7%, p=0.015).

Figure 3:1 Frequency of socioeconomic status score in this cohort of 464 acute stroke patients



The above figure represents the socioeconomic status of the TIA / stroke cohort (464 patients) studied in this chapter. The socioeconomic status score is derived from Scottish Neighbourhood Statistics (28). This is a Scottish government programme using information on education, employment, environment, health, housing, crime & access to services to generate small area statistics on socioeconomic status. It provides an index of socioeconomic status for each Scottish post code - 1 (lowest socioeconomic status) to 6505 (highest socioeconomic status). The cohort studied in this chapter is more deprived than

the Scottish Population, just over a third of this cohort is in the lowest 10% of socioeconomic status in Scotland.

Table 3:1 Univariate analysis of vascular risk factors and quartiles of socioeconomic status (SES) in 464 acute TIA / stroke patients

	All Patients n=464	Lowest quartile (lowest SES) n=118	Second quartile n=114	Third quartile n=116	Top quartile (highest SES) n=116	p
Age, mean (SD), yr	68.6 (14.1)	63.9 (14.1)	69.1 (14.3)	69.8 (13.7)	72.1 (12.9)	**<0.0001**
Gender, male:female	233:235	55:63	56:58	53:63	65:51	0.231
Current Smoker	153 (32.8%)	50 (42.4%)	39 (34.5%)	39 (33.6%)	25 (21.6%)	**0.001**
Family History of IHD /CVA	54 (11.6%)	13 (11%)	9 (8%)	16 (13.8%)	16 (13.8%)	0.069
*Admission Systolic BP, mean (SD), mmHg	148 (27) {n=393}	144 (27) {n=99}	150 (29) {n=101}	151 (26) {n=99}	147 (27) {n=94}	0.330
*Admission Diastolic BP, mean (SD), mmHg	82 (18) {n=393}	78 (16) {n=99}	81 (17) {n=101}	84 (21) {n=99}	82 (18) {n=94}	0.125
†Later Systolic BP, mean (SD), mmHg	136 (22) {n=425}	134 (20) {n=102}	137 (25) {n=108}	135 (19) {n=108}	139 (24) {n=107}	0.290
†Later Diastolic BP, mean (SD), mmHg	76 (13) {n=425}	76 (12) {n=102}	75 (15) {n=108)	76 (13) {n=108}	78 (14) {n=107}	0.403
Admission Cholesterol, mean (SD), mmol	4.6 (1.3) {n=310}	4.8 (1.4) {n=83}	4.6 (1.3) {n=70}	4.5 (1.2) {n=76}	4.4 (1.3) {n=81}	0.334
Admission HDL Cholesterol, mean (SD), mmol	1.29 (0.6){n=278}	1.36 (0.92) {n=76}	1.22 (0.41) {n=63}	1.28 (0.42) {n=65}	1.26 (0.43) {n=74}	0.565
Admission Blood Glucose, median (IQR), mmol/L	6 (5.3-7.1) {n=380}	6.0 (5.3-7.5){n=98}	6.2 (5.3-7.3) {n=99}	5.9 (5.3-6.7) {n=94}	5.8 (5.3-7.1) {n=89}	0.723
History of diabetes	80 (17.1%)	21 (17.8%)	24 (21.2%)	15 (12.9%)	20 (17.2%)	0.530
History of hypertension	254 (54.4%)	51 (44.3%)	64 (57.1%)	74 (63.8%)	64 (55.2%)	**0.059**
History of raised lipids	247 (52.9%)	57 (49.1%)	68 (60.2%)	61 (52.6%)	61 (52.6%)	0.888
History of cerebrovascular disease	131 (28.1%)	30 (25.4%)	38 (33.6%)	33 (28.4%)	30 (25.9%)	0.849
History of ischaemic heart disease	147 (31.5%)	37 (31.4%)	32 (28.3%)	37 (31.9%)	41 (35.3%)	0.425
History of peripheral vascular disease	25 (5.4%)	5 (4.2%)	5 (4.4%)	7 (6%)	8 (6.9%)	0.307
History of revascularisation	40 (8.6%)	5 (4.2%)	10 (8.8%)	9 (7.8%)	16 (13.8%)	**0.018**

History of ischaemic vascular disease	241 (51.6%)	52 (44.1%)	57 (50.4%)	66 (56.9%)	66 (56.9%)	**0.03**
History of congestive cardiac failure	14 (3%)	2 (1.7%)	3 (2.7%)	5 (4.3%)	4 (3.4%)	0.329
History of chronic pulmonary disease	66 (14.1%)	20 (16.9%)	19 (16.8%)	13 (11.2%0	13 (11.2%)	0.131
History of moderate-severe renal disease	11 (2.4%)	3 (2.5%)	0 (0%)	5 (4.3%)	3 (2.6%)	0.491
History of dementia	26 (5.6%)	6 (5.1%)	6 (5.3%)	7 (6.0%)	7 (6.0%)	0.708
Charlson index of co-morbidity, median (IQR)	5 (2-8)	0 (0-1)	1 (0-1.5)	0 (0-1)	0.5 (0-1)	0.852
No of medications, median (IQR)	0 (0-1)	5 (2-9)	7 (2-9)	6 (3-8)	5 (3-8)	0.527

* BP checked at admission, or if outpatient taken at time of symptoms

† BP checked at discharge or 1 week after admission (whichever first) or before instigation of antihypertensives. If outpatient this is BP checked at time of clinic assessment.

Results of continuous variables are mean (SD) and categorical variables given as number (%), except where stated. Non-normally distributed variable results are shown as median (IQR). Data are complete unless otherwise stated. Statistical analysis is by Analysis of Variance (normally distributed continuous variables), Kruskal-Wallis H test (non-normally distributed continuous variables) or Chi-squared test (categorical variables).

Table 3:2 Association of socioeconomic status and other basic clinical characteristics with cigarette smoking

	B	S.E.	Wald	p	OR	95.% CI for OR	
						Lower	Upper
Gender	.263	.212	1.533	.216	.769	.507	1.166
Age	.051	.008	40.371	.000	1.053	1.036	1.069
Socioeconomic status	.191	.096	3.983	.046	1.211	1.003	1.461
Ischaemic vascular disease	.024	.216	.012	.913	.977	.639	1.492
Constant	-3.037	.711	18.267	.000	.048		

Binary logistic-regression analysis (enter logistic regression) was performed with the dependent variable current smoker / not current smoker; independent variables were gender, age, quartiles of socioeconomic status and history of ischaemic vascular disease (ischaemic heart disease, cerebrovascular disease or peripheral vascular disease).

Table 3:3 Association of socioeconomic status and other basic clinical characteristics with diastolic blood pressure at admission

	Unstandardised Coefficients		Standardized Coefficients	t	p
	B	Std. Error	Beta		
Constant	82.103	5.304		15.479	.000
Gender	1.349	1.823	.038	.740	.460
Age	-.131	.067	-.102	-1.950	.052
Stroke severity (mNIHSS)	.297	.200	.076	1.480	.140
Socioeconomic status	2.023	.838	.125	2.415	.016

Linear regression analysis (enter) was preformed with the dependent variable diastolic blood pressure; independent variables were gender, age, quartiles of socioeconomic status and modified National Institute of Health Stroke Score.

Table 3:4 Association of socioeconomic status and other basic clinical characteristics with history of hypertension

	B	S.E.	Wald	p	OR	95.0% CI for OR	
						Lower	Upper
Gender	-.125	.195	.415	.520	1.133	.774	1.660
Age	.034	.008	19.135	.000	1.034	1.018	1.050
Smoker	.030	.220	.018	.892	1.030	.670	1.584
Socioeconomic status	-.085	.088	.927	.336	.919	.773	1.092
Constant	2.250	.591	14.480	.000	9.489		

Binary logistic-regression analysis (enter logistic regression) was performed with the dependent variable history of hypertension / no history of hypertension; independent variables were gender, age, quartiles of socioeconomic status and current smoking.

Table 3:5 Association of socioeconomic status and other basic clinical characteristics with history of ischaemic vascular disease

	B	S.E.	Wald	p	OR	95.0% CI for OR	
						Lower	Upper
Gender	-.380	.340	1.250	.264	.684	.351	1.331
Age	-.018	.014	1.637	.201	.982	.956	1.010
Socioeconomic status	.490	.435	1.269	.260	1.633	.696	3.830
Smoker	-.288	.158	3.320	.068	.750	.550	1.022
Constant	4.470	1.124	15.816	.000	87.354		

Binary logistic-regression analysis (enter logistic regression) was performed with the dependent variable history of ischaemic vascular disease / no history of ischaemic vascular disease; independent variables were gender, age, quartiles of socioeconomic status and current smoking.

Table 3:6 Association of socioeconomic status and other basic clinical characteristics with history of revascularisation

	B	S.E.	Wald	p	OR	95.0% CI for OR	
						Lower	Upper
Gender	-.431	.346	1.554	.213	.650	.330	1.280
Age	-.016	.014	1.298	.255	.984	.957	1.012
Socioeconomic status	.312	.162	3.707	.054	1.336	0.994	1.876
Smoker	.453	.438	1.070	.301	1.573	.667	3.714
Constant	4.545	1.147	15.698	.000	94.195		

Binary logistic-regression analysis (enter logistic regression) was performed with the dependent variable history of revascularisation / no history of revascularisation; independent variables were gender, age, quartiles of socioeconomic status and current smoking.

Health Care Access and Utilisation

Table 3:7 shows a univariate analysis of SES and stroke service provision. In this cohort 170 (36.4%) of patients were treated as outpatients, 77.6% of inpatients were treated in a stroke unit and 4% of inpatients had thrombolysis. Twenty five patients referred for TIA / stroke outpatient assessment did not attend their appointment; following review of the referral information, 12 referrals were thought likely to have had a recent TIA or acute stroke. Therefore 12 of 170 (7.1%) of outpatients who were likely to have a recent acute cerebrovascular event did not attend their appointment.

On univariate analysis TIA / stroke patients in the lowest socioeconomic quartile, compared to patients in the uppermost quartile, were less likely to undergo neuroimaging with a CT or MRI brain scan (82.2% versus 90.5%, p=0.036) or to have an ECG (72% versus 87.1%, p=0.003); they were also less likely to attend their outpatient appointment (81.8% versus 98%, p=0.001). There was no association of SES with other aspects of service provision or utilisation including echocardiogram, carotid imaging and admission to a geographically defined stroke unit or thrombolysis. The lack of association between SES and stroke unit care remained after stratification for stroke severity.

Multivariate analysis examining whether any of the above univariate associates of SES were also independent associates was undertaken (Tables 3:8 and 3:9). SES was not an independent associate of failing to have a CT or MRI scan or ECG when age, stroke severity and which hospital attended were controlled for. TIA and stroke patients were less likely to have neuroimaging or an

electrocardiogram if they were treated as an outpatient or were seen at Glasgow Royal Infirmary. In addition those who did not have a neuroimaging were more likely to be men. The numbers of patients who did not attend their outpatient appointment was small and did not allow for meaningful multivariate analysis.

Table 3:7 Univariate analysis of stroke care access / utilisation and quartiles of socioeconomic status (SES) in 464 acute TIA / stroke patients

	All patients n=464	Lowest quartile (lowest SES) n=118	Second quartile n=114	Third quartile n=116	Top quartile (highest SES) n=116	p
Treated as an inpatient	297 (63.6%)	70 (59.3%)	81 (71.1%)	78 (67.2%)	65 (56%)	0.507
Outpatients who did not attend	12 (7.1%) {n=170}	9 (18.8%) {n=48}	2 (6.1%) {n=33}	0 (0%) {n=38}	1 (2.0%) {n=51}	**0.001**
Treated on a Stroke Unit	228 (77.6%) {n=294}	52 (76.5%) {n=68}	62 (76.5%) {n=81}	63 (80.8%) {n=78}	50 (76.9%) {n=65}	0.778
Arrived within Thrombolysis window	49 (24.6%) {n=199}	14 (36.8%) {n=38}	9 (16.4%) {n=55}	12 (21.4%) {n=56}	14 (28%) {n=50}	0.638
Had Thrombolysis	12 (6%) {n=199}	2 (5.3%) {n=38}	4 (7.3%) {n=55}	5 (8.9%) {n=56}	1 (2.0%) {n=50}	0.554
Did not have a CT	59 (12.6%)	21 (17.8%)	15 (13.2%)	11 (9.5%)	11 (9.5%)	**0.036**
Did not have a carotid imaging	191 (40.9%)	54 (45.8%)	46 (40.4%)	50 (43.1%)	39 (33.6%)	0.098
Did not attend carotid imaging outpatient appointment	4 (1.4%) {n=281)	3 (4.5%) {n=66}	1 (1.4%) {n=70}	0 (0%) {n=67}	0(0%) {n=77}	**0.02**
Did not have echo	343 (73.4%)	86 (72.9%)	80 (70.2%)	86 (74.1%)	89 (76.7%)	0.401
Did not attend echo outpatient appointment	20 (15.9%) {n=126}	8 (25%) {n=32}	8 (23.5%) {n=34}	2 (6.5%) {n=31}	2 (7.1%) {n=28}	**0.017**
Did not have ECG	86 (18.4%)	33 (28%)	20 (17.5%)	17 (14.7%)	15 (12.9%)	**0.003**
Did not have BP checked at time of Stroke	70 (15%)	19 (16.1%)	12 (10.5%)	17 (14.7%)	22 (19%)	0.399
Did not have cholesterol checked	154 (33%)	35 (29.7%)	43 (37.7%)	40 (34.5%)	35 (30.2%)	0.941
Did not have blood glucose checked	84 (18%)	20 (16.9%)	14 (12.3%)	22 (19%)	27 (23.3%)	0.109
History of ischaemic vascular disease but no antiplatelet or warfarin	23 (5.9%)	7 (5.9%)	4 (3.5%)	8 (6.9%)	4 (3.4%)	0.648
History of ischaemic vascular disease but no statin	63 (13.5%)	12 (10.2%)	13 (11.4%)	22 (19%)	16 (13.8%)	0.194

Results of categorical variables are given as number (%), except where stated. Data are complete unless otherwise stated. Statistical analysis is Chi-squared test.

Table 3:8 Association of socioeconomic status and other basic clinical characteristics with not having a CT or MRI scan

	B	S.E.	Wald	p	OR	95.0% CI for OR	
						Lower	Upper
Gender (men)	.695	.340	4.173	.041	2.004	1.029	3.906
Age	-.007	.013	.289	.591	.993	.967	1.019
Stroke severity (mNIHSS)	.055	.079	.482	.488	1.057	.905	1.234
Socioeconomic status	.070	.156	.201	.654	1.072	.790	1.456
Outpatient	3.072	.528	33.837	.000	21.739	2.174	390.625
Hospital	1.257	.351	12.848	.000	3.514	1.768	6.988
Constant	5.785	1.522	14.454	.000	325.279		

Binary logistic-regression analysis (enter logistic regression) was performed with the dependent variable did not have CT or MRI / did have CT or MRI; independent variables were gender, age, modified National Institute of Health Stroke Score, quartiles of socioeconomic status, whether treated as inpatient or not and hospital where treated.

Table 3:9 Association of socioeconomic status and other basic clinical characteristics with not having an ECG

	B	S.E.	Wald	p	OR	95.0% CI for OR	
						Lower	Upper
Gender	.218	.301	.525	.469	1.243	.690	2.242
Age	.008	.012	.473	.492	1.008	.985	1.031
Stroke severity (mNIHSS)	.018	.060	.094	.759	1.019	.906	1.145
Socioeconomic status	.204	.141	2.089	.148	1.227	.930	1.618
Outpatient	3.061	.434	49.680	.000	21.277	9.091	50.000
Hospital	.815	.261	9.773	.002	2.258	1.355	3.763
Constant	4.085	1.228	11.073	.001	59.448		

Binary logistic-regression analysis (enter logistic regression) was performed with the dependent variable did have ECG / did not have ECG ; independent variables were gender, age, modified National Institute of Health Stroke Score, quartiles of socioeconomic status, whether treated as inpatient or not and hospital where treated.

Severity and Outcome

Table 3:10 shows a univariate analysis of socioeconomic status and outcome. In this group of acute stroke patients 63 (13.6%) of patients had a total anterior circulation stroke (TACS), 145 (31.3%) had a TIA and 40 (8.6%) died during their acute hospital admission. The median mNIHSS was 3 (IQR 2-5). This is a relatively low overall mNIHSS but reflects the fact that a large proportion of the group were diagnosed with TIA.

On univariate analysis TIA / stroke patients in the lowest SES quartile were less likely to have had a TIA (30.5% versus 42.2%, p=0.02); there was also a non-significant tendency for this group to have a more severe stroke (lowest quartile SES median mNIHSS 4 [IQR 2-6] versus highest quartile 3[1-5], p=0.057). There was no significant association of SES with in-hospital mortality or the proportion with a TACS, or other stroke sub-type.

Multivariate analysis with age, gender, history of ischaemic vascular disease, smoking and SES in the model and stroke severity as the dependent is shown (Table 3:11). This shows that SES is an independent associate of stroke severity (beta=-0.133, p=0.05). A model (Table 3:12) with the same variables but with TIA as the dependent showed that TIA is independently associated with SES, but it is those in the higher SES groups who are more likely to have a TIA (beta=-0.278, p=0.04).

Table 3:10 Univariate analysis of severity / outcome and quartiles of socioeconomic status (SES) in 464 acute stroke / TIA patients

	All patients n=464	Lowest quartile (lowest SES) n=118	Second quartile n=114	Third quartile n=116	Top quartile (highest SES) n=116	p
mNIHSS, median (IQR)	3 (2-5)	4 (2-6) {n=115}	4 (2-6) {n=111}	3 (2-5) {n=116}	3 (1-5) {n=116}	0.057
TACS stroke Subtype	63 (13.6%)	17 (14.4%)	18 (15.8%)	15 (12.9%)	13 (11.2%)	0.383
TIA	145 (31.3%)	36 (30.5%)	24 (21.1%)	36 (31%)	49 (42.2%)	**0.02**
Died in hospital	40 (8.6%)	11 (9.3%)	8 (7%)	13 (11.2%)	8 (6.9%)	0.788

Results of non-normally distributed continuous variables are median (IQR) and categorical variables given as number (%), except where stated. Data are complete unless otherwise stated. Statistical analysis is by Kruskal-Wallis H test (non-normally distributed continuous variables) or Chi-squared test (categorical variables).

Table 3:11 Association of socioeconomic status and other basic clinical characteristics with mNIHSS

	Unstandardised Coefficients		Standardized Coefficients	t	p
	B	Std. Error	Beta		
Constant	2.951	1.245		2.371	.018
Age	.041	.016	.130	2.606	.009
Gender	-.363	.408	-.041	-.889	.375
Socioeconomic status	-.536	.185	-.137	-2.890	.004
Smoker	.489	.463	.052	1.056	.291

Linear regression analysis (enter logistic regression) was preformed with the dependent variable modified National Institute of Health Stroke Score; independent variables were age, gender, quartiles of socioeconomic status and smoking.

Table 3:12 Association of socioeconomic status and other basic clinical characteristics with TIA

	B	S.E.	Wald	p	OR	95.0% CI for OR	
						Lower	Upper
Gender (female)	.485	.207	5.475	.019	1.624	1.082	2.437
Age	.007	.008	.913	.339	1.008	.992	1.023
Socioeconomic status	-.278	.095	8.538	.003	.757	.629	.913
Smoker	.479	.229	4.393	.036	1.616	1.031	2.532
Constant	.917	.599	2.340	.126	2.502		

Binary logistic-regression analysis was preformed with the dependent variable TIA / no TIA; independent variables were age, gender, quartiles of socioeconomic status and smoking.

Discussion

Vascular Risk Factors

This study shows an independent association between current smoking and SES in TIA and stroke patients. This association has also been demonstrated in three other studies (38;46;57), but two studies (41;49) showed no association. These results add weight to the argument that increased rates of smoking explain part of the association between stroke disease and SES.

However the overall rate of smoking in this cohort is less then in other similar Scottish acute stroke cohorts. Between 1991 and 1998 Aslanyan et al (57) found a smoking rate of 45%. In 2004/5 Sellars et al (137) found a rate of 46.6%. Our overall rate was 32.8% with no statistical difference between the number of inpatient and outpatient smokers. It appears that rates are reducing over time and this may partly be due to the ban on smoking in public places in Scotland in 2006 (140). However this study is unable to determine whether smoking rates may be reducing amongst those of low SES.

This study has demonstrated that TIA and stroke occurs at a younger age in subjects from lower socioeconomic groups. It is not clear what causes this premature appearance of cerebrovascular disease but it may be secondary to increased smoking rates, early life influences or a, so far, unidentified factor.

The burden of pre-existing vascular risk factors in this cohort was similar to Sellers et al (137) but compared to the earlier Aslanyan et al (57) there was generally a greater prevalence, particularly for diabetes (17% versus 4%) and raised lipids (53% versus 14%).

No independent association was found between SES and any pre-existing vascular risk factors or vascular history, other than a history of revascularisation. No evidence was found to support the hypothesis that high blood pressure or poorly controlled hypertension is more common in stroke subjects from low socioeconomic groups. These findings are consistent with the findings of others studies considering stroke patients (41;57) including McFadden (52). McFadden is a recent study of stroke and SES, also from the United Kingdom. They found that none of the classical vascular risk factors explain the association between stroke and SES, in contrast to our study they found no link with smoking. However this study differs significantly from ours as it was a longitudinal population study with people were invited to participate. Vascular risk factors were assessed at baseline by questionnaire, SES was based on occupation and stroke was ascertained though hospital record linkage and death registry. However Kuper et al (38) found an association between SES and both diabetes and hypertension and Hart et al (37) found an association between SES and blood pressure measured prior to TIA / stroke and history of IHD.

In the stroke subgroup analyses there was an association between SES and family history of IHD / TIA & stroke with those in the higher SES group having a greater frequency of family history. However family history was poorly recorded in this study with 74% of patients having no reference to family history in their notes. This subgroups analysis therefore involves a small number of patients and should

be interpreted with caution. However it may be that those in the low SES group have less knowledge of family history or are less likely to be asked about it.

Those who have the lowest SES appeared less likely to have a revascularisation procedure but this should also be considered cautiously as the number of revascularisation procedures was very small.

None of the traditional vascular risk factors measured at the time of admission were significantly associated with SES. However glucose and lipids, for all inpatients and many outpatients, was checked during, or shortly after, an acute stroke. The first BP was always checked at the time of acute TIA or stroke. Therefore the results may not reflect the usual BP, glucose or lipids. A later BP was also recorded but there was no association between that BP and SES. It was therefore considered that a pre-existing history of hypertension, hyperlipidaemia and diabetes, as detailed above, was more critical when considering a possible burden of vascular risk factors amongst low SES TIA and stroke patients.

No association between SES and co-morbid illness was found, as measured by the modified Charlson Index and medication count. These methods are validated measures of co-morbidity (132;141;141). However it is well known that those who are socioeconomically disadvantaged are more likely to suffer ill health (30) and a more comprehensive assessment of general ill-health may have demonstrated an association. This may have included other measures of comorbidity such as simply considering the number of chronic diseases or using functional ability as a measure of comorbidity.

In this cohort our hypothesis that those in the lower SES group would have a greater burden of vascular risk factors is not apparent, with only current smoking being more common.

Health Care Access and Utilisation

It is encouraging that in this study those with low SES have equitable access to stroke unit care. The overall rate of stroke unit care in this cohort, 78%, compares favorably to the overall Scottish figure of 64% (142) and the Western European figure of less than 50% (143). The overall rate of thrombolysis of 4% in this study compares to a recent study in Holland where the thrombolysis rate of hospitals varied between 6 and 22% (144), there are no recent Scottish figures for thrombolysis. There was also apparent equity in thrombolysis provision, although relatively few patients were thrombolysed and these results should be interpreted cautiously.

There have been few studies looking at multiple aspects of stroke provision and SES and there is no consensus. In cardiac disease there is evidence of an “inverse care law” (145), where the availability of good health care is least where it is most needed i.e. an area of social deprivation. In Stroke McKevitt et al (71) found no socioeconomic inequality in stroke provision although Jakovlijevic et al (45) found that lower SES patients were less likely to have appropriate imaging, see a specialist and be treated in a university hospital. McKevitt et al took place in England where free comprehensive medical care is available to all but Jakovlijevic et al took place in Finland where this is not the case. Cesaroni et al

(51) noted that studies which show a link between SES and poor outcome after stroke usually take place in countries where there is private health care. It may be that when low SES patients are treated in a free health care system, or where stroke units are the standard of care, the potential adverse factors which contribute to a poorer outcome e.g. unequal access to health care, are overcome.

The apparent univariate association of reduced rates of neuroimaging / having an electrocardiogram with SES appeared to be partly explained by regional differences in stroke care. However correction for these factors in multivariate analyses may conceal true associations. Glasgow Royal Infirmary serves the lowest SES population of the three hospitals in this study and it is possible that the organisation and planning of TIA and stroke is given a lesser priority (financial or otherwise) in areas of low SES. In addition the association between younger age and reduced access to investigation may be driven by lower SES in the younger subjects.

There was also a univariate association between low SES and failure to attend outpatient appointments but small numbers did not allow any further analysis. This potential failure to utilise available health care in subjects from lower socioeconomic groups might contribute to poorer stroke outcome.

Severity and Outcome

This study shows an association between increased stroke severity and SES. Although there is increasing evidence on the association between SES and stroke,

the link with stroke severity has not often been considered. Arrich et al (56) and Aslanyan et al (57) found a link with stroke severity but both of these studies examined inpatients only. This is the first study considering both TIA / stroke inpatients and outpatients to show a link between SES and stroke severity.

Although there was an association with TIA and SES, with those who have a lower SES being more likely to have a TIA, there was no association with other stroke subtypes. It is possible that referral patterns may confound this association. Those who have a low SES may be less likely to approach their doctor with TIA symptoms or they may be less frequently referred to secondary care. However it was not within the scope of this study to consider what happens in the community.

This study was not designed to consider outcome although in-hospital death was recorded. However there was no clear link of stroke outcome with SES. This would be in keeping with Lofmark et al (129) who followed patients up for 28 days and found no link between short term mortality and SES.

Strengths / Weaknesses

The main strength of this study is that data was gathered prospectively from consecutive stroke and TIA patients, including both hospital admissions and outpatients. Previous studies in this area have often been retrospective and did not consider outpatient TIA and stroke. There may be criticism of considering TIA and stroke together but we consider they are a continuum of the same disease process and the definition of TIA as symptoms less than 24 hours

somewhat arbitrary. However we acknowledge that there may be different issues for TIA versus stroke in relation to SES. Additionally the diagnosis of TIA and stroke was a clinical one and made by several different stroke physicians across three sites. There may have been a small risk of ascertainment bias but the stroke physicians work to the same clinical criteria and it is unlikely there has been any significant ascertainment bias in the diagnosis of TIA / stroke or vascular risk factors.

The study was based in the stroke unit of each of the three hospitals but there was regular liaison to other wards / departments to pick up outliers. There may have been cases of stroke or TIA which occurred in the community and were not bought to the attention of primary care, or not referred to hospital, but it was not within the scope of this study to establish how many cases were not known to secondary care. However there is increasing public awareness of the need to seek attention for stroke symptoms and general practitioners are actively encouraged to promptly refer any symptoms of concern to the three hospitals in this study. We are therefore confident that the sample provides a comprehensive representation of patients experiencing stroke or TIA during the study period and that there would be little reporting bias.

The data was collected from medical records and therefore relied on patients recall and physicians recording of past medical history and current clinical details. A potential weakness may be incomplete data but this data collection was done prospectively in the acute setting and every effort was made by the clinical team to collect comprehensive information. We also did not consider all potential vascular risk factors and the inclusion of body mass index, exercise level and alcohol consumption may have strengthened results but the major

conventional vascular risk factros were included. We were also unable to consider other potential factos which may explain the link between socioeconomic status and stroke such as birth weight and childhood nutrition but it was always out intention to consdier only vascualr risk factors and provision of stroke care.

Based on our original power calculations of BP, the intention was to recruit a further 35 patients and it is acknowledged that when considering admission BP the study may be slightly underpowered. It should also be acknowledged that additional power calcualtions to determine the sample size required for multivariate regression analyses were not done but for this reason the number of independent variable entered into the multivariate models was kept low.

The small area derived SES index (28) used in this study is based on the most recent Scottish census (2001). This uses multiple factors to derive an index of SES. There are concerns that this method for measuring SES is based on small populations and not individuals. However each small area in the Scottish Neighbourhood Statistics database contains less than one thousand people and had been widely adopted by Scottish agencies examining SES.

This cohort is particularly socioeconomically disadvantaged compared to the overall Scottish population, 78% of this cohort are in the lower half of Scottish SES. This cohort may not be generalisable to the Scottish population but we believe the narrower spread of SES in this cohort will have, if anything, underestimated the difference between low and high SES.

Summary

In summary this study has demonstrated that smoking is likely to be a factor in the association between SES and stroke. However other vascular risk factors, pre-existing vascular disease and general co-morbidity are not more common in TIA / stroke subjects from lower SES groups. Additionally this study has shown that socioeconomically disadvantaged TIA / stroke patients are younger and tend to have a more severe stroke. This finding is concerning and means that research is critical to further clarify the association between SES and stroke incidence and severity. Public health campaigns regarding smoking cessation should be directed at lower SES groups. Such strategies might involve “social marketing”, the concept where marketing strtegies are used for social good such as improved health, and there is evidence that mass media campaigns can reduce smoking rates (146). Alternatively allowing smoking cessation information/personnel access to work places or health centres may be helpful in low SES areas. There is also a suggestion that payment to encourage smoking cessation may reduce smoking rates in low SES areas but there is evidence from a Cochrane Meta-analysis (147) that incentives, including financial incentives, do not improve the likelyhood os smoking cessation.

Lastly this work demonstrated that TIA / stroke patients with a low SES have equal access to stroke unit care. This is reassuring but more research is needed to establish whether access to all aspects of stroke care is equal, particularly for stroke patients who are not entitled to free comprehensive health care.

Chapter 4:

Socioeconomic Status, Oral Health and Acute Stroke

Introduction

Poor oral health and in particular periodontitis (inflammatory disease affecting the tissues that surround and support the teeth) is an established risk factor for stroke (76-79) and lower SES is known to be linked to poor oral health (81;82). It is theorised that dental disease might be part of the explanation for the association between stroke and SES.

Saliva plays a vital role in maintaining oral health and is necessary for normal speech and swallowing (148). Acute stroke is likely to be associated with reduced salivary production through mechanisms such as dehydration, poor oral hygiene and medication use although currently there is no evidence in this area. A dry mouth (xerostomia) is potentially uncomfortable and leads to increased risk of periodontal disease and dental caries (149). Xerostomia may also contribute to dysphagia. Additionally, in acute stroke patients it has been proposed that reduced saliva may lead to abnormal oral bacterial colonisation; combined with dysphagia these changes in oral flora may be a mechanism for aspiration pneumonia (150).

Poor oral health (151;152) and a reduced salivary flow rate (153) have been observed in long-term stroke survivors and post stroke disability is the main determinant of long-term poor oral health (151;152). However nothing is known about salivary flow after acute stroke.

The aim was to determine salivary flow after acute stroke, factors associated with xerostomia including oral flora, and the clinical consequences of

xerostomia. In addition the oral health of stroke patients from different SES groups was examined.

Aims

- To determine if SES is associated with poor oral health in acute stroke
- To determine salivary flow rate after acute stroke
- To identify factors associated with dry mouth after acute stroke
- To examine the clinical consequences of xerostomia

Methods

Subjects

A prospective cohort study of consecutive admissions to the Glasgow Royal Infirmary during a 17-month period (June 2004 to November 2005) was conducted. Patients with first or recurrent ischaemic or haemorrhagic stroke within 7 days of admission to hospital were included. Patients at >7 days after admission and those who, after further investigation, had a diagnosis other than

stroke were excluded. The diagnosis of stroke was based on clinical features supported by brain CT or MRI scanning. There were no other exclusion criteria. Permission to participate was sought from all patients (consent) or their caregivers if patients did not have capacity to consent (assent). The study had the approval of the Multi-Centre Research Ethics Committee of Scotland.

Procedures

Salivary flow rates (unstimulated were measured at the bedside on a single occasion by Salivette® sampling as described by Sweeney et al (154). The insert from a sterile Salivette® (Sarstedt Ltd, Leicester, UK) was placed beneath the tongue for 30 seconds. It was then removed and replaced in the inner tube of the Salivette®, and the unit was sealed. On arrival at the laboratory the Salivette® was centrifuged at 4000 rpm in a bench-top centrifuge (Centaur 1, Fisons, Crawley, Sussex, UK), and the volume of saliva that collected in the outer tube was measured by means of a microsyringe.

The condition of the oral cavity on inspection was assessed with the Oral Assessment Guide (OAG) (155). The OAG is an assessment tool generating a score of 8-24. There are eight assessment domains each scoring 1 to 3; voice, swallow, lips, tongue, saliva, mucous membranes, gingiva and teeth or dentures. A normal mouth would score 8 with higher scores representing increasingly severe oral disease.

The presence of oral yeasts, coliforms, and *Staphylococcus aureus* was determined by imprint culture; a sterile foam pad (1×1 cm) was applied to the

sample site tongue for 5 seconds. The pad was then used to sequentially inoculate individual plates of Sabouraud's agar and Pagano Levin agar for yeast culture, mannitol salt agar for *Staphylococcus aureus* and MacConkey agar for coliforms. The plates were transported to the laboratory within 3 hours for incubation and processed according to standard methods.

The presence and severity of dysphagia were determined by an algorithm which incorporated both a water swallow test (WST) (156) and different consistencies of test. The WST involved progressively larger amounts of water: 3×5-mL teaspoons, 10 mL, 20 mL, and then 50 mL of water from a cup with the procedure being discontinued at any stage if there was evidence of coughing, choking, voice change or (increased) breathlessness. Subjects unable to perform the WST or with any of these observations were categorised as failing this assessment. Detailed clinical assessment of swallowing was undertaken with reference to the Logemann screening procedure for oro-pharyngeal dysphagia (157) and the Daniels scale for determining severity of dysphagia (158). The Logemann screening procedure includes 28 variables in 5 categories with each variable marked either safe or unsafe. The Daniels scale uses 6 clinical features; dysphonia, dysarthria, abnormal cough, abnormal gag reflexes, cough after swallow and voice change after swallow to predict dysphagia severity.

The premorbid modified Rankin Scale (mRS) (159), details of prior medical history and admission medication were recorded. Severity of neurological impairment was assessed using the NIHSS (160) and post-stroke disability with the mRS. Cognitive function was also assessed using the Abbreviated Mental Test (AMT) (161).

SES was derived from post-codes using Scottish Neighbourhood Statistics (28). This is a Scottish government programme using information on education, employment, environment, health, housing, crime & access to services to generate small area statistics on SES. It provides an index of SES for each Scottish post code from 1 (lowest SES) to 6505 (highest SES). The patient's post code was recorded and then a Scottish Neighbourhood index generated for each of the patients in this study. About a thousand people live in each of these post code areas.

Participants were also followed up at 3 months after stroke to determine survival and residual disability (mRS). Post-stroke pneumonia (Mann criteria) (162), urinary tract infections (UTIs) and other bacterial infections were also recorded. All assessments were performed by a single research assistant, other than the assessments of infection which were recorded by an independent medical assessor. All assessors were unaware of the results of the salivary flow test. A flow chart of patient recruitment and 3 month follow-up is shown in Figure 4:1.

Lynsey Bowie (Research Speech & Language Therapist) was responsible for collecting all of the above information but I generated the SES data and did the analysis detailed in the rest of this chapter.

Data Analysis and Statistical Methods

This study is a secondary analysis of a study that investigated the risk factors for post-stroke pneumonia.

Data was analyzed with the Statistical Package for the Social Sciences software (version 15.0). The characteristics of those patients with dry mouth (salivary flow <1ul/min) were compared to those with salivary flow 1-120 and >120ul/min. Normally distributed continuous variables were described as mean and SD and analysed by Analysis of Variance. Non-normally distributed continuous variables were described as median (IQR) and analysed by the Kruskal-Wallis H test. Categorical variables were described as number (and percentage) and analyzed by the Chi-squared test. All probabilities are 2-tailed. Statistical significance was accepted at $p<0.05$.

To examine the independent risk factors for dry mouth after acute stroke, binary logistic-regression analysis (forward logistic regression) was performed with the dependent variable dry mouth (salivary flow <1ul/min) or not dry mouth (salivary flow >1ul/min). The clinical outcomes of those patients with dry mouth (salivary flow <1ul/min) were compared to those without a dry mouth (salivary flow >1ul/min). The clinical outcomes were all categorical variables and were analyzed by the Chi-squared test.

The SES index was analysed in quartiles. A univariate analysis was undertaken using Analysis of Variance for normally distributed continuous variables, Kruskal-Wallis H test for non-normally distributed continuous variables and the Chi-squared test for categorical variables. For this analysis results for continuous variables are given as mean (SD) and for categorical variables given as number (%). Non-normally distributed variable results are shown as median (IQR).

Results

Oral status assessment (including salivary flow rates) was performed in 368 out of 412 eligible patients. Eligible patients were those with a diagnosis of new, acute stroke within the last 7 days who consented to participate. Full oral status assessment was not completed in patients who were too unwell to safely allow the assessments. The 368 patients were assessed at a median of 4 days (IQR, 3 to 6 days) after stroke. The study population had a mean age of 67 years (range, 30 to 97 years) with half the patients being male. The major diagnosis was cerebral infarction (n=346, 94%). There was a wide range of stroke severity (NHISS median 5 [IQR 2,11]) and stroke subtypes with 57 (15.5%) classified as total anterior circulation syndrome, 119 (32.3%) as partial anterior circulation syndrome, 140 (38%) as lacunar circulation syndrome and 42 (11.4%) as posterior circulation syndrome (136).

Of the 368 patients that had oral health assessments 356 had a post code from which a SES score could be derived. The frequency of this score is shown in Figure 4:3. The catchment area of Glasgow Royal Infirmary is one of the most deprived in Scotland with nearly 60% of this cohort being in the lowest 10% of Scottish SES. These patients were analysed in quartiles of SES. However none of the markers of oral health available in this study showed a significant univariate association with SES (Table 4:4). This oral health as measured by the OAG, oral flora, total tooth loss (either full dentures or no teeth without dentures) and salivary flow.

In total, 225 of 368 (61.1%) had no detectable salivary flow as measured by the Salivette® (Figure 4:2). In univariate analysis (Table 4:1) pre-stroke factors

associated with xerostomia included older age, female gender, number of prescribed medicines and pre-stroke disability. A history of alcoholism was associated with higher salivary flow. Low SES was not associated with dry mouth. Post-stroke factors associated with xerostomia included stroke severity (NIHSS and mRS), cognitive impairment (AMT) and raised C-reactive protein (CRP). There was also an association with UTI (confirmed by mid-stream urine culture) and other infections but not with pneumonia. There was no association with maximum temperature.

There was no significant association of xerostomia with oral cavity health or with bacterial colonisation; there was a significant association with oral colonisation with *Candida glabrata* but not with *Candida albicans* (Table 4:2). Low salivary flow rate was associated with increased proportion with cough or throat clearing after swallow (Logemann assessment) as evidence of aspiration (p=0.027), however there were no other significant univariate associations of dry mouth with other markers of dysphagia (Table 4:2). There was no statistically significant increase with dry mouth in risk of death or death or disability at 3 months.

Further analysis of the data by binary logistic-regression analysis (Table 4:3) was conducted. The dependent variable was dry mouth (no salivary flow) / no dry mouth (≥1 ul/min) and independent binary variables were gender, age, number of medications, history of alcohol excess, pre-morbid mRS score, log CRP, NIHSS score, mRS score, AMT score, UTI and Other Infections and *Candida glabrata*. The independent associates of dry mouth were pre-stroke disability (mRS), UTI and oral colonisation with *Candida glabrata*. A binary logistic regression analysis was also performed with the dependent variable cough or throat clearing after

swallow (evidence of aspiration on the Logemann assessment), and NIHSS score and salivary flow (categorised as <1, 1-120 and >120 ul/min); on this analysis higher NIHSS score was associated with increased risk of aspiration (multivariate OR 1.19; 95% CI 1.13, 1.25; p<0.001) however there was no significant association of reduced salivary flow (OR 1.27; 95% CI 0.85, 1.89; p=0.24).

Figure 4:1 Flow chart of patient recruitment and 3 month outcome

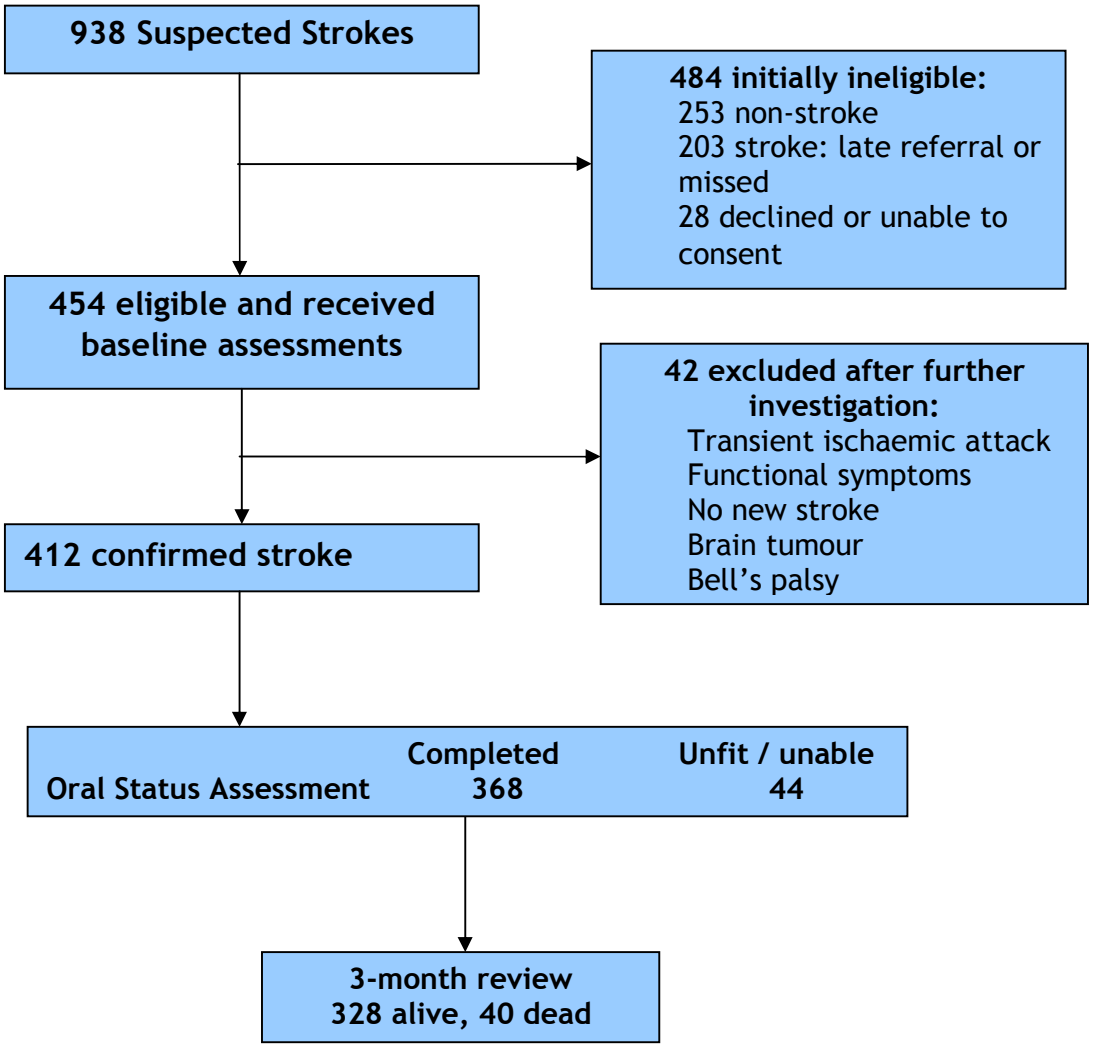


Figure 4:2 Percentage of acute stroke patients with no salivary flow, reduced salivary flow (1-120 uL/min) and normal salivary flow (>120uL/min)

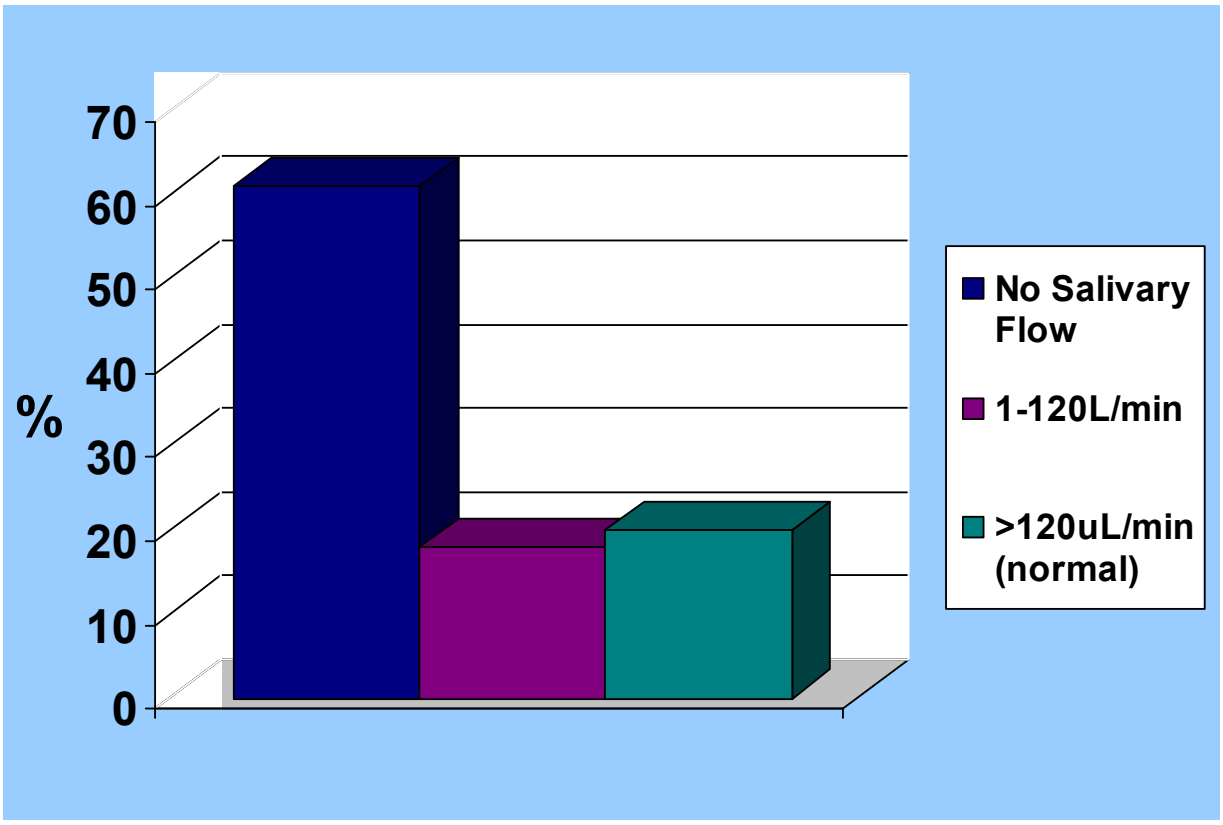


Table 4:1 Clinical characteristics and basic laboratory investigation in acute stroke patients; categorised by salivary flow.

Patient characteristics	Salivary flow			p
	<1uL/min	1-120uL/min	>120uL/min	
Number	225 (61.1%)	69 (18.1%)	74 (20.1%)	
Age years	68.4 (13.9)	68.6 (13.3)	62.4 (13.9)	**0.004**
Male:female	96:129	34:35	54:20	**<0.001**
Pre-stroke characteristics				
Socioeconomic status (in lowest 10% of Scottish popn)	132 (58.7%)	34 (49.3%)	46 (62.2%)	0.260
No. of medications, median (IQR)	6 (3,9), n=219	5 (3,5), n=65	5 (1,7), n=71	**0.006**
Smoker	102 (45.3%)	38 (55.1%)	36 (48.6%)	0.362
Diabetes mellitus	46 (20.4%)	9 (13.0%)	10 (13.5%)	0.214
Alcohol Excess	40 (17.8%)	14 (20.3%)	25 (33.8%)	**0.014**
Pre-stroke mRS, median (IQR)	0 (0,2), n=207	0 (0,0), n=62	0 (0,0), n=67	**<0.001**
Post-stroke characteristics				
NIHSS, median (IQR)	5 (3,9), n=224	4 (2,10),	3 (2,6.5), n=73	**0.015**
mRS, median (IQR)	3 (2,4)	3 (2,4)	2 (1.8-4)	**0.001**
AMT score, median (IQR)	8 (4,9.5), n=223	8 (4.6,9.9), n=68	9 (7,10), n=71	**0.036**
C-reactive protein mg/L, geometric mean (95% CI)	24.5 (20.5-29.3)	20.4 (15.3-27.6)	14.1 (11.3-17.7)	**0.004**
Maximum temperature	36.9 (0.8)	36.8 (1.5)	36.9 (0.7)	0.655
Serum urea, mmol/L	6.6 (2.9)	6.3 (3.1)	6.1 (3.1)	0.362
Pneumonia	33 (15%), n=220	10 (14.5%)	9 (12.5%)	0.837
Urinary Tract Infection (confirmed with mid-stream urine culture)	43 (19.2%), n=224	6 (8.7%)	2 (2.7%)	**0.001**
Other infection	30 (13.5%), n=222	6 (8.8%), n=68	2 (2.7%), n=74	**0.028**

Results of continuous variables are mean (SD) and categorical variables given as number (%), except where stated. Data are complete unless otherwise stated. Statistical analysis is by Analysis of Variance (normally distributed continuous variables), Kruskal-Wallis H test (non-normally distributed continuous variables), and Chi-squared test (categorical variables).

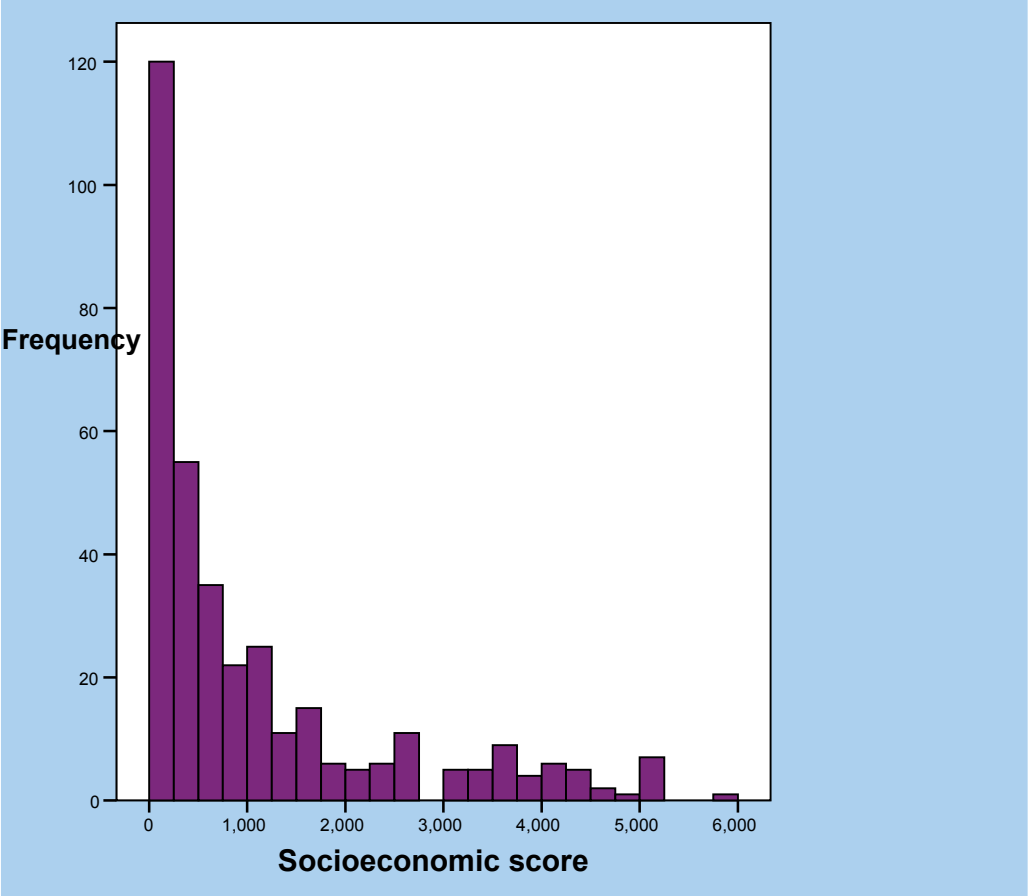
IQR = interquartile range

mRS = modified Rankin Scale

NIHSS = National Institutes of Health Stroke Scale

AMT = Abbreviated Mental Test

Figure 4:3 Frequency of socioeconomic status score in this cohort of 356 acute stroke patients (those who had oral assessment and post code available)



The above figure represents the socioeconomic status of the acute stroke cohort (356 patients) studied in this chapter. The socioeconomic status score is derived from Scottish Neighbourhood Statistics (28). This is a Scottish government programme using information on education, employment, environment, health, housing, crime & access to services to generate small area statistics on socioeconomic status. It provides an index of socioeconomic status for each Scottish post code - 1 (lowest socioeconomic status) to 6505 (highest socioeconomic status). The cohort studied in this chapter has a lower

socioeconomic status than the Scottish Population – nearly 60% of this cohort is in the lowest 10% of socioeconomic status in Scotland.

Table 4:2 Univariate analysis of oral health and quartiles of socioeconomic status (SES) in 356 acute stroke patients

	All patients n=356	Lowest quartile (lowest SES) n=91	Second quartile n=87	Third quartile n=89	Top quartile (highest SES) n=89	p
Oral Assessment Guide score, median (IQR)	10 (8-12)	10 (8-12.25)	10 (8.75-13)	10 (8.5-13)	10 (8-12)	0.209
Gram Negative Bacteria	41 (11.5%)	13 (14.3%)	8 (9.2%)	11 (12.4%)	9 (10.1%)	0.528
Gram Positive Bacteria	47 (13.2%)	10 (11%)	14 (16.1%)	16 (18%)	7 (7.9%)	0.652
Candida albicans	161 (45.2%)	41 (45.15)	44 (50.6%)	32 (36%)	44 (49.4%)	0.955
Candida glabrata	52 (14.6%)	10 (11%)	13 (14.9%)	15 (16.9%)	14 (15.7%)	0.331
Total tooth loss	168 (47.2%)	41 (45.1%)	34 (39.1%)	45(50.6%)	48(53.9%)	0.110
Salivary Flow (ul/min), median (IQR)	0 (0-100)	0 (0-100)	0 (0-100)	0 (0-100)	0 (0-100)	0.878

Results of non-normally distributed continuous variables are median (IQR) and categorical variables given as number (%), except where stated. Data are complete unless otherwise stated. Statistical analysis is by Kruskal-Wallis H test (non-normally distributed continuous variables) and Chi-squared test (categorical variables)

Table 4:3 Oral health status, oral bacterial and fungal colonisation, and markers of dysphagia in acute stroke patients; results categorised by salivary flow

	Salivary Flow			p
	<1uL/min	1-120uL/min	>120uL/min	
Number	225 (61.1%)	69 (18.1%)	74 (20.1%)	
Oral Assessment Guide score	10 (7,13), n=223	10 (8,12), n=69	9 (8,12), n=74	0.225
Dentures	110/223 (49.3%)	38/67 (56.7%)	41/74 (55.4%)	0.454
Oral bacteria / fungi				
Gram-positive bacteria	35 (15.6%)	7 (10.1%)	9 (12.2%)	0.468
Gram-negative bacteria	30 (13.3%)	7 (10.1%)	8 (10.8%)	0.714
Candida albicans	105 (46.7%)	35 (50.7%)	27 (36.5%)	0.191
Candida glabrata	42 (18.7%)	6 (8.7%)	4 (5.4%)	**0.006**
Markers of dysphagia				
Failed WST	53 (23.6%)	13 (18.8%)	9 (12.2%)	0.101
Logemann total score	1 (0,5), n=218	1.5 (0,5), n=68	1 (0,3.5), n=73	0.252
Logemann oral stage disorder	72/218 (33%)	23/68 (33.8%)	21/73 (28.8%)	0.763
Logemann pharyngeal delay	44/218 (20.2%)	13/68 (19.1%)	6/73 (8.2%)	0.062
Logemann pharyngeal stage disorder	24/218 (11.0%)	10/68 (14.7%)	6/73 (8.2%)	0.471
Logemann aspiration	42/218 (19.3%)	17/68 (25%)	6/73 (8.2%)	**0.027**
Daniels severity of dysphagia score	0 (0,1), n=218	0 (0,2), n=68	0 (0,1), n=73	0.622

Results of continuous variables are median (interquartile range) and categorical variables given as number (%). Statistical analysis is by Kruskal-Wallis H test (non-normally distributed continuous variables), and Chi-squared test (categorical variables).

WST = Water Swallow Test

Table 4:4 Independent predictors of dry mouth after acute stroke

	B	S.E.	Wald	p	OR, 95% CI
Step 1					
Pre-stroke mRS	0.644	0.164	15.437	<0.0001	1.904, 1.381-2.626
Constant	0.271	0.133	4.157	0.041	1.311
Step 2					
Candida glabrata	1.415	0.466	9.226	0.002	4.117, 1.652-
Pre-stroke mRS	0.656	0.167	15.439	<0.0001	10.262
Constant	1.529	0.449	11.620	0.001	1.927, 1.389-2.673
					4.615
Step 3					
UTI	1.116	0.476	5.493	0.019	3.052, 1.2-7.761
Candida glabrata	1.394	0.468	8.863	0.003	4.031, 1.610-
Pre-stroke mRS	0.618	0.169	13.381	<0.0001	10.093
Constant	3.646	1.024	12.669	<0.0001	1.856, 1.333-2.585
					38.308

Binary logistic-regression analysis (forward logistic regression) was performed with the dependent variable dry mouth (no salivary flow) /no dry mouth (≥1 ul/min); independent variables were gender, age, number of medications, history of alcohol excess, pre-stroke modified Rankin Scale (mRS), log C-reactive protein, modified National Institutes of Health Stroke Scale, post-stroke mRS, Abbreviated Mental Test, Urinary Tract Infection (UTI), Other Infection and *Candida glabrata*.

Discussion

Dry mouth is common, being found in over 60% of acute stroke patients. There is a wide range of normal unstimulated salivary flow rates but the average rate in a healthy population is 300uL/min. For the purposes of this study 120uL/min was taken as the cut-off between normal and reduced salivary flow (163). Using this cut-off, just 20% of patients had a normal salivary flow. The average age of this cohort was 67 years and the prevalence of xerostomia in the general adult population over 65 is estimated at 30% (164). This would however include both people with no salivary flow and those with reduced salivary flow who have subjective dry mouth.

In this study there was no association between SES and poor oral health in acute stroke patients. Although there is a known association between SES and dental disease (81;82) in well community dwelling adults it is likely that acute illness influences salivary flow, oral flora and oral health. However tooth loss may be a marker of pre-existing oral health but there was no significant association with SES. Tooth loss represents the extreme end of dental disease and a measure of early periodontitis may have been more appropriate. A large prospective cohort study of stroke incidence would be a more appropriate way to establish if oral health may explain some of the association between SES and stroke.

The pre-stroke associates of xerostomia (older age, female gender, number of medications, pre-stroke disability) are in keeping with what is already known. Xerostomia increases with age (165) and women have lower salivary flow rates than men (166). Many drugs are known to reduce salivary flow (167) and so it is not surprising that the use of multiple medications is associated with post-stroke

dry mouth. The association of xerostomia and disability may be because of the reduced ability to maintain oral hygiene or the association of increasing disability with age or co-morbid illness, but pre-stroke disability was also an independent associate when age and medication number was controlled for. The finding that those with a history of alcohol excess were less likely to have dry mouth is clinically counterintuitive and has not previously been noted in the literature. However the association with alcohol is not seen in the multivariate analysis.

Post-stroke factors associated with xerostomia on univariate analysis included stroke severity, cognitive impairment, and raised CRP. Possible mechanisms for the association of dry mouth and stroke severity include inability to maintain oral hygiene, dysphagia and dehydration. However no association between dry mouth and oral health (as measured by the Oral Assessment Guide) was found. There is also no association between xerostomia and dehydration as shown by blood urea. However blood urea is a relatively poor maker of dehydration therefore it is not possible to completely exclude dehydration as an explanation. Cognitive impairment, although significant as a univariate association, was not an independent predictor in multivariate analysis but it may be that in acute stroke cognitive impairment reflects stroke severity. The univariate association of xerostomia and CRP may reflect stroke severity and / or an infective process which could lead to fever and dehydration. Although no association between dry mouth and pneumonia was found there was an association with UTI and other infections. Other infections include all other infections recorded clinically during the inpatient stay and included cellulitis and conjunctivitis. It may be the apparent association of dry mouth and infective processes other then pneumonia reflect stroke severity but a common process such as dehydration may be the

explanation and this needs further investigation. UTI was also independently associated with xerostomia reinforcing a likely common process.

Early after acute stroke there was no significant association of xerostomia with oral cavity health, bacterial colonisation or *Candida albicans*; however there was a significant association with oral colonisation with *Candida glabrata*. *Candida glabrata* was also one of the independent associates found on multivariate analysis. This emerging oral opportunistic pathogen is now the second most commonly found *Candida* spp. isolated from the oral cavity (after *Candida albicans*) (168). It has also been shown in patients with Sjorgen's syndrome that *Candidia glabrata* is more common as salivary flow decreases (169). Symptoms of clinical oral candidosis were not assessed and the clinical significance of this finding is not clear. It was thought unlikely that the association with *Candida glabrata* is causal. There is no pre-existing evidence to suggest *Candidia* species have any influence on salivary flow. It has also been shown in patients with Sjorgen's syndrome that *Candidia glabrata* is more common as salivary flow decreases. It is likely that the increase in *Candida Glabrata* is a consequence of dry mouth rather than a cause.

Saliva is known to be necessary for normal swallow (148) but this study did not find any convincing association between dry mouth and dysphagia, as measured by the water swallow test, Logemann score and Daniels score. In univariate analysis the cough / throat clearing component of the Logemann score, suggesting aspiration, was associated with dry mouth; however when corrected for severity of stroke this link was attenuated and became non-significant.

Although patients with dry mouth were no more likely to have pneumonia or poorer outcome in terms of death or disability, xerostomia still has the potential

to cause morbidity. Dry mouth is uncomfortable, and over a period of time may lead to poor oral health (170).

This study had a number of strengths. We believe it to be the first prospective cohort study of an acute stroke population reporting on salivary flow and oral health. It aimed to be comprehensive in its scope and provided ongoing data by means of follow-up to 3 months. The assessments of oral health were thorough and used validated assessment tools. The results of other assessments were blind to knowledge of salivary flow rate.

However there are also some potential weaknesses. Not all consecutive admissions were included because of researcher leave and late referral. Furthermore, some patients were not well enough to undertake the oral assessments, but any bias is likely to have led to an underestimate of the prevalence of xerostomia, due to exclusion of the very ill. Another limitation is that salivary flow was only was measured on one occasion and to ensure the acute stroke patients in this study had optimal clinical care the study investigations had to be done opportunistically. Salivary flow changes in response to food and oral fluids but although salivary flow rate vaires significantly between subjects it is thought to be reasonably consistent in an individual. However repeated testing at a standardised time may have provided more reproducible results. It is known that persisting xerostomia leads to significant problems with oral health in the elderly (171), and act as a contributor to dysphagia in the medium to longer term and ideally there would have been further follow-up including salivary flow. Bedside assessments of the water swallow test and Logemann and Daniels scores in assessment of post-stroke dysphagia and risk of aspiration were used. While these are validated

tools, they do have limitations; instrumental examinations such as videofluroscopy and endoscopic evaluation of swallowing may be more accurate means of assessing dysphagia.

Further research is needed to establish the time course of xerostomia in acute stroke and the longer-term association with patient discomfort, oral health and dysphagia as well as the link between poor oral health, stroke and SES. The association of Urinary Tract Infection and *Candida glabrata* with dry mouth needs to be confirmed in other study cohorts. The role of possible interventions including active hydration, prudent use of medicines, regular oral hygiene and artificial saliva also requires investigation.

Summary

There was no association between SES and poor oral health as measured in this study but oral health may still be part of the explanation of the association between SES and acute stroke and this needs further investigation. Dry mouth amongst acute stroke patients is very common. There is an association with pre-stroke disability and Urinary Tract Infection. There is also a link with oral *Candida glabrata* colonisation, although the clinical relevance of this uncertain. In the acute phase after stroke there is no convincing association of dry mouth with dysphagia or pneumonia. However dry mouth is likely to be of symptomatic importance and should be considered when caring for acute stroke patients.

Chapter 5:

Long-term follow-up of the PROSPER study cohort: a feasibility study

Introduction

Cognitive decline and disability in old age are major public health issues, with both having major affects on social functioning and quality of life as well as significant health and social care costs. The prevalence of dementia rises markedly with increasing age, from approximately 1.5% of 65-69 year olds to 30% in those aged over 90 (10). The risk of physical disability also increases dramatically with advancing age, with approximately 13% of the over-80s categorised as having a 'severe' problem in the UK national census (172).

Cognitive decline and disability in older age have many common risk factors. Increasingly it is recognised that vascular disease is an important and potentially preventable contributor to both. There has been considerable interest in the possibility that the vascular components of dementia and disability may be preventable. However the PROSPER (118) study showed no protective effect of pravastatin on cognition or activities of daily living in those aged 70–82 years with a history of, or risk factors for, vascular disease. However the duration of follow-up was 3.2 years and this may have been too short to demonstrate any benefit.

The PROSPER dataset also includes a biobank (blood samples) which allows investigation into disease mechanisms in older age. Plausible targets include inflammatory pathways and haemostatic function. A number of laboratory analyses have already been made, particularly markers of inflammation and

haemostasis (CRP, Interleukin-6, D-Dimer), and these results were available for use in this study.

There is increasing evidence that low SES, measured by income (86-88), occupation (89) and small area statistics (90), is a risk factor for cognitive impairment and dementia. There is also an established association between lower levels of education and increased risk of cognitive impairment and dementia (83;84). However this is due in part to the known correlation of education with cognitive test performance at all ages. Additionally education is likely to contribute to “brain reserve”. This is a multifactorial phenomena related to complex brain activity which allows preserved cognitive function despite underlying neurodegenerative pathology.

We aimed to establish a methodology for determining long-term, post trial, cognitive function and ability to perform activities of daily living in PROSPER survivors. This would build on the existing dataset by gathering additional information on cognitive function and activities of daily living as medium to long-term outcomes and would allow assessment of the contribution of new and emerging risk factors, including socio-economic status, for cognitive impairment and disability in old age.

Aims

- Feasibility of re-contacting Scottish PROSPER survivors.

- Feasibility of using of telephone questionnaires to determine prevalence of dementia and disability in survivors.

- Feasibility of using written questionnaires to relatives / carers to determine prevalence of dementia and disability in survivors.

- To determine the likely proportion of subjects surviving with dementia.

- To determine the likely proportion of subjects surviving with disability.

Methods

We planned to re-contact Scottish survivors of the PROSPER study and their carers or relatives. Scottish data suggests an expected annual mortality rate of 78/1000 for women and 83/1000 for men aged 75-79. A total of approximately 2,200/2,520 of the Scottish cohort were alive at the end of study follow up in May 2002. It was estimated, with a subsequent annual death rate of around 8% that approximately 50% of subjects would still be alive at 6 years after the trial finished, giving a cohort of approximately 1,100 Scottish PROSPER participants alive and available for review.

Our previous study experience of telephone contact suggested that it should be possible to gather cognitive data on around 74% of available subjects (173). Therefore if the whole Scottish cohort were screened we would anticipate obtaining information on cognitive function and disability in 800 surviving subjects.

We performed a pilot study of 300 PROSPER recruits to establish feasibility and refine the above estimates of numbers of subjects that are likely to be available for study. This study had approval from Multi-Centre Research Ethics Committee of Scotland and as part of the consent process from the original PROSPER study participants had agree to be recontacted for follow-up.

Screening process

A random sample of 300/2,520 of the original Scottish PROSPER cohort was selected. This sample was computer generated random numbers and was done by the Robertson Centre for Biostatistics, Glasgow University. This was independent of the clinical research team. The Robertson Centre for Biostatistics also identified subjects who died during the original study, or who had been identified in record linkage as deceased after the randomised observation period of the study.

The subject's general practitioner (GP) was contacted by letter asking them to confirm the subject was alive and if the subject was suitable for contact. If the subject could not be contacted the GP was asked to say why (e.g. dementia, dysphasia, subject preference, withdrawal of consent from PROSPER study) and if there was a relative or carer that could be contacted instead. The GP was also asked if the subject had cognitive impairment. Lastly the GP was asked to provide contact details for the subject or relative. If there was no response from

the GP within 2 weeks this was followed up by a single reminder telephone call to the general practice.

If the subject was suitable for review a letter was sent to the subject offering a telephone interview in one week's time. A contact telephone number was provided to allow subjects to opt out if they wish, or change the date or time of the telephone interview.

Telephone contact with the subject involved initial verbal consent for the study. The subject was then asked about their residence, cohabittees and any formal home care support. Current drug treatment was recorded, including use of statins. Disability was then assessed by telephone administration of the Barthel index (174) and short Instrumental Activities of Daily Living (IADL) questionnaire (175). The modified Telephone Interview of Cognitive Status (TICSm) was also administered screen for cognitive impairment. This is a 21-item questionnaire with a maximum score of 40 (176;177).

When a subject was not suitable for contact and a relative was available a postal questionnaires were sent to the relative. This consisted of the short form of the Informant Questionnaire on Cognitive decline in the elderly (IQCODE) (178), the Barthel index (174) and short IADL questionnaires (175). There were also questions on the type of residence, formal home care support, and any cohabitees. Carers or relatives who did not return the postal questionnaire within 2 weeks were reminded by a single telephone call.

Significant cognitive impairment / dementia was diagnosed using the 'or' rule, using any of the following;

a) Subjects scoring <21 on TICSm (179).

b) Relative / carer giving a score of ≥3.38 on the IQCODE (178).

c) Subjects who are deemed by the GP as unsuitable for telephone review due to dementia.

d) Subjects with dementia recorded as a primary or secondary cause of death.

e) Subjects who scored <24 on the Mini-Mental State Exam (MMSE) on final PROSPER follow-up who had subsequently died.

Data Analysis and Statistical Methods

All-cause mortality was analysed for those not lost to follow-up (n=267). Cognitive impairment was analysed for those who had died or who were alive and contacted for the pilot study (n=226). Cognitive impairment was defined as subject scoring <21 on the TICSm or relative / carer giving a score of ≥3.38 on the IQCODE or subject who the GP deemed to have dementia or dementia recorded as primary or secondary cause of death or subject scoring <24 on their final MMSE during the PROSPER trial and who subsequently died. Statistical analysis included calculation of the univariate logistic regression odds ratio for placebo versus pravastatin. An adjusted odds ratio was also calculated adjusting for known risk factors age, gender, years of education (as a measure of SES), history of vascular disease, history of diabetes mellitus, smoking status, alcohol

intake and systolic blood pressure. For each odds ratio, 95% confidence intervals and p-values are reported.

There is no simple cut-off to diagnose disability, therefore the change in Barthel and IADL from study baseline to pilot study follow-up were analysed as continuous variables. Decline in disability were compared between placebo and pravastatin groups using linear models adjusting for the baseline measure of the variable. A further model was fitted adjusting for the known risk factors above. Adjusted least square means and standard errors are reported for each treatment group and mean differences with 95% confidence intervals and p-values are also given.

Information on home circumstances and support were collected for those subjects who were contacted or whose relative / carer were contacted (n=81) and compared between placebo and pravastatin. Baseline characteristics were reported comparing the PROSPER survivors who developed significant cognitive impairment (n=28) to survivors who did not (n=63). Continuous variables are presented as mean and standard deviation and categorical variables are summarised as number and percentages. Continuous variables are analysed by two sample t-test and categorical variables by Chi-square test or Fisher's Exact test as appropriate. The distributions of the baseline variables Interleukin-6, CRP and D-dimer were markedly skewed and therefore log-transformed. The summary results presented for these variables are therefore their geometric mean and standard deviation, and the log transformed variables were analysed.

Results

A flow chart of recruitment and data collection is given as figure 1. Of the 300 Scottish PROSPER subjects randomly selected, 135 had died and 132 were known to be alive at the time of review, at an average of 6yrs 10 months after study completion.

Of the 300 subjects in our random sample, survivorship was established through record linkage and GP contact in 267 (89%), therefore we had no information on the mortality status of 33 subjects; 17 of the 148 allocated to placebo and 16 out of 152 in the pravastatin group were lost to follow-up. Of the 132 known survivors long-term follow-up data were obtained for 78 subjects who had telephone interview, 10 subjects with GP diagnosis of dementia, and 3 subjects unsuitable for personal follow-up for whom carers provided questionnaire data; this gave a total of 91/132 (69%) survivors who could be categorised as having significant cognitive impairment or not. In total outcomes (dead / alive, cognitive status established for survivors) were determined in 226/300 (75.3%).

The proportion of deaths, over a mean of 10 years follow-up (including trial duration of 3.2 years and post-trial follow-up period of 6yrs 10 months), was very similar in the placebo and pravastatin groups (Table 5:1) at around 50%. There was no significant difference in the proportion of the sample who developed significant cognitive impairment / dementia. In total 17/112 (15.9%) of the placebo group and 19/114 (16.7%) allocated to pravastatin fulfilled criteria for significant cognitive impairment.

In survivors there was a decline in Barthel by approximately 1 point (20-point scale) over the 10 years from study baseline, and for IADL a decrease by 1.7 points (14-point scale), with no significant differences between the placebo and pravastatin groups (Table 5:2, Figure 5:2). Home circumstances and the level of home support services for survivors are summarised in Table 5:3; there were no significant differences between the placebo and pravastatin groups. Similarly there were no significant differences in the current use of commonly prescribed drugs between the placebo and pravastatin groups (Table 5:4).

The baseline characteristics of the 28 PROSPER survivors who developed significant cognitive impairment were compared with 63 survivors who did not (Table 4). Cognitive impairment associated with older age at baseline ($p=0.007$). There was no association with years of education.

Figure 5:1 Study flow chart - Recruitment and data collection for the PROSPER study long-term follow-up

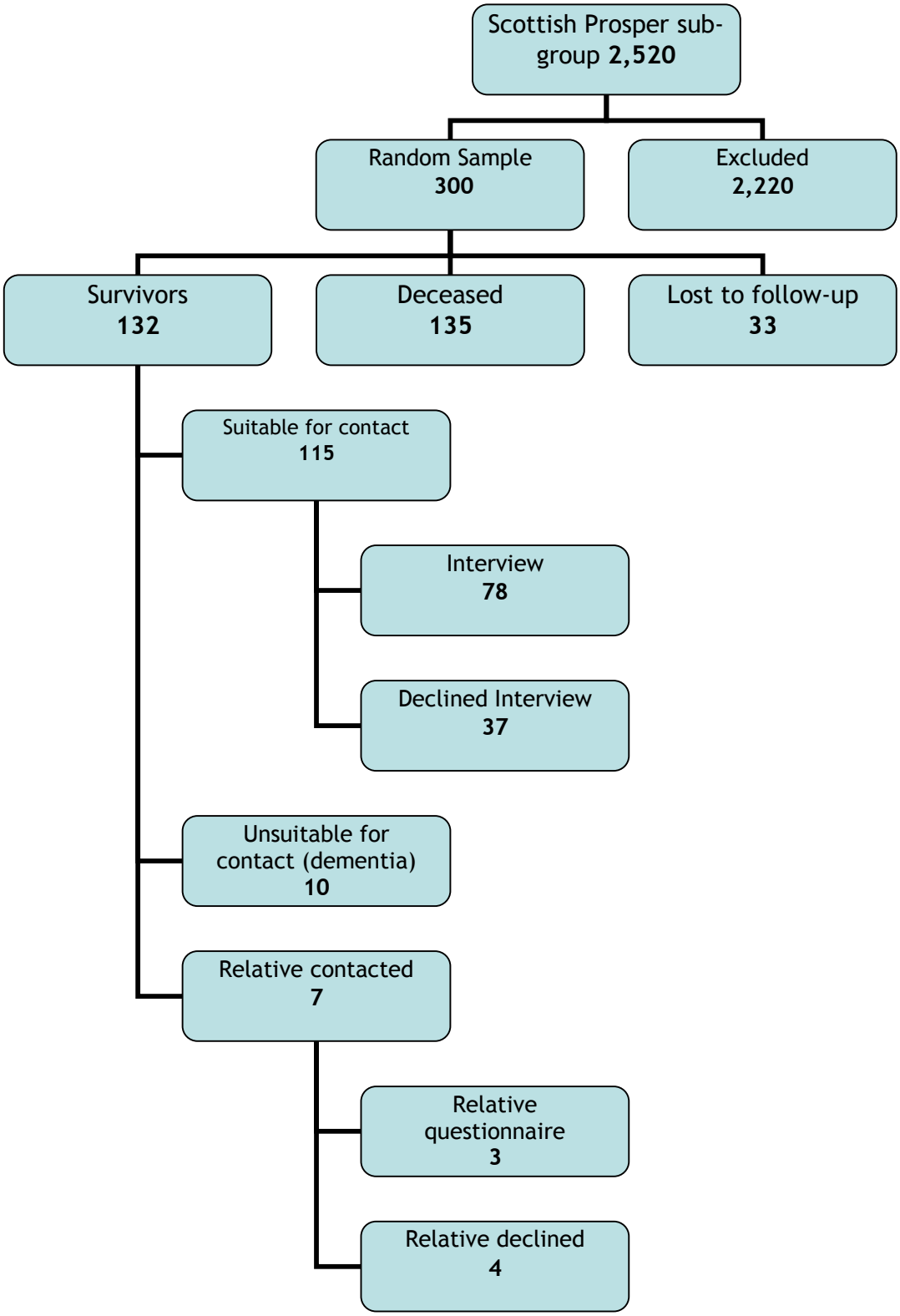


Table 5:1 Cognitive function, deaths and loss to follow up

	Total (n=300)	Placebo (n=148)	Pravastatin (n=152)
TICSm <21/40	16/78	6/38	10/40
TICSm score (mean, SD)	24.5 (5.3)	25.3 (5.6)	23.7 (4.9)
IQCODE ≥ 3.38	2/3	2/3	0/0
GP diagnosis of dementia	10	6	4
MMSE <24/30 at final PROSPER review and died prior to follow-up	4	1	3
Dementia recorded as cause of death	4	2	2
Alive and no evidence of significant cognitive impairment	64	34	30
Total with known significant cognitive impairment (of the 226 those who had died or who were alive and contacted)	36/226 (15.9%)	17/112 (15.2%)	19/114 (16.7%) Unadjusted OR 1.12 (0.55, 2.28) p=0.76 *Adjusted OR 1.13 (0.54, 2.35) p=0.74
Total deceased (of the 267 who were not lost to follow-up)	135/267 (50.6%)	65/131 (49.6%)	70/136 (51.5%) Unadjusted OR 1.08 (0.67, 1.74) p=0.76 *Adjusted OR 1.00 (0.59, 1.69) p=0.99

TICSm = Telephone Interview Cognitive Status (modified).

IQCODE = Informant Questionnaire on Cognitive decline in the Elderly.

MMSE = Mini-Mental State Examination.

Odds Ratio = OR

*Adjusted for age, gender, education, history of vascular disease, diabetes mellitus, smoking status, alcohol intake and systolic blood pressure.

Table 5:2 Change in basic activities of daily living (Barthel index) and instrumental activities of daily living (IADL)

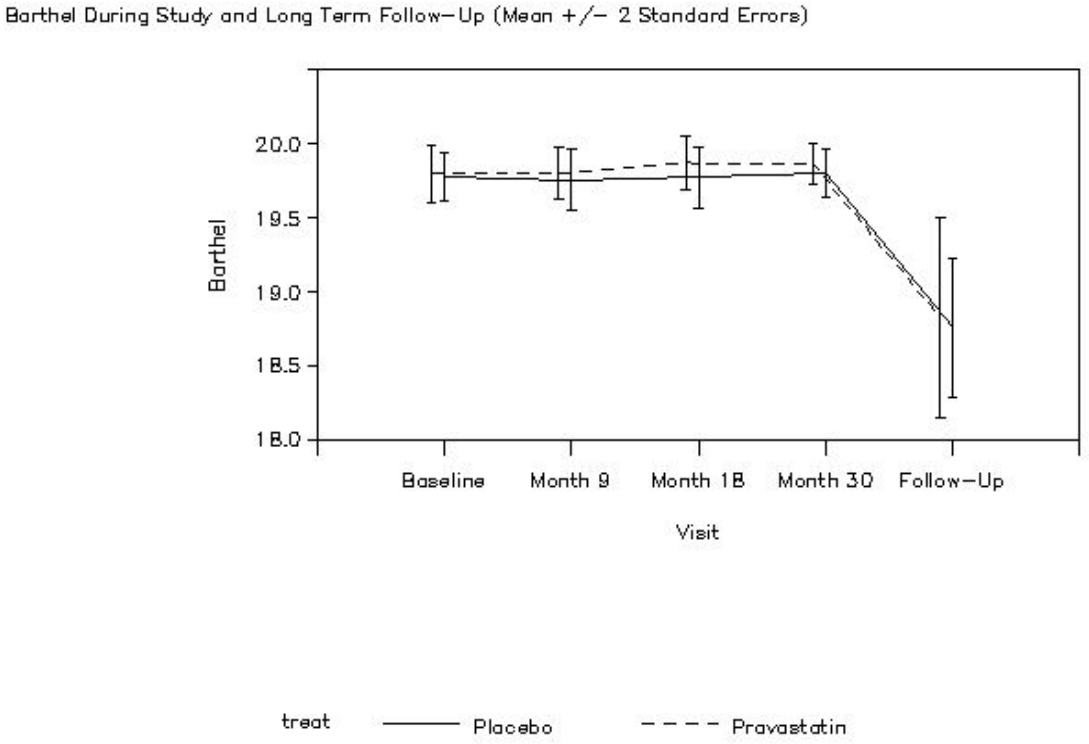
		Placebo (n=41) (mean, SEM)	Pravastatin (n=40) (mean, SEM)	Difference Pravastatin-placebo (95% CI)	P
Change in Barthel Index	Adjusted (model 1)	-1.02 (0.27)	-0.98 (0.28)	-0.05 (-0.82, 0.72)	0.90
	Adjusted (model 2)	-0.63 (0.55)	-0.41 (0.56)	-0.21 (-1.04, 0.62)	0.61
Change in IADL	Adjusted (model 1)	-1.65 (0.35)	-1.71 (0.36)	0.06 (-0.94, 1.06)	0.91
	Adjusted (model 2)	-1.43 (0.71)	-1.39 (0.73)	-0.04 (-1.11, 1.03)	0.94

Model 1 adjusted for baseline measure of variable (Barthel Index or IADL as appropriate).

Model 2 adjusted for age, gender, education, history of vascular disease, diabetes mellitus, smoking status, alcohol intake and systolic blood pressure.

IADL = Instrumental Activities of Daily Living.

Figure 5:2 Activities of daily living (Barthel index) and instrumental activities of daily living during the PROSPER study (baseline to month 30) and at long-term review of survivors (7 years after study completion); n=41 subjects allocated to placebo, n=40 allocated to pravastatin.



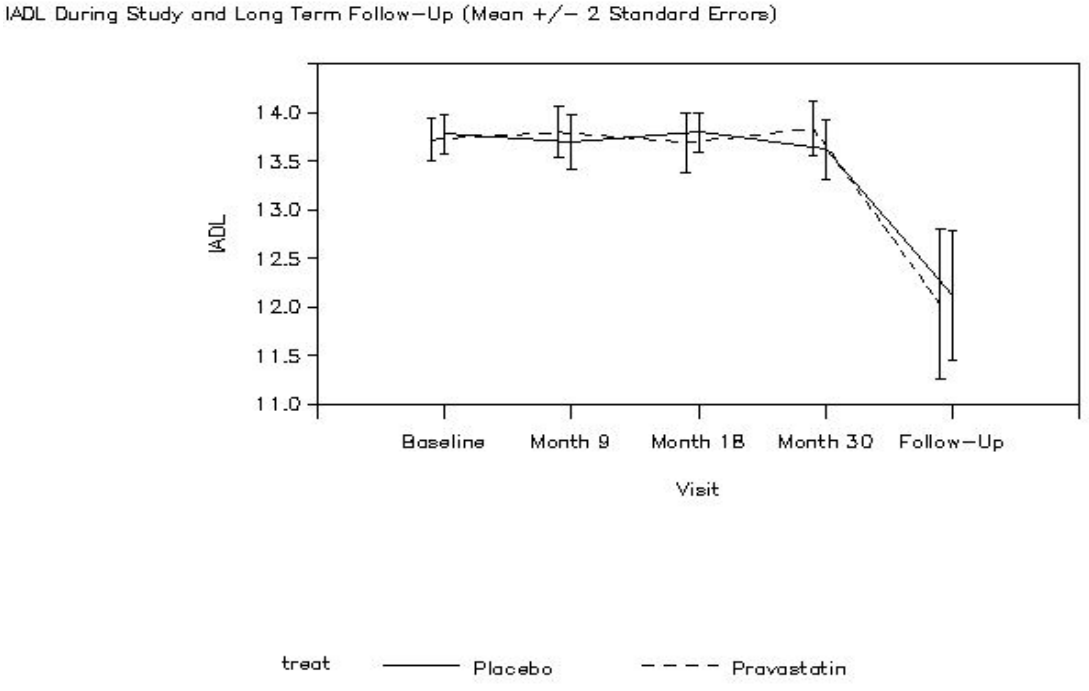


Table 5:3 Home circumstances and support at long-term review of survivors (6 years after study completion)

Home circumstances / support	Placebo (n=41)	Pravastatin (n=40)	p
Alone in own home	20 (48.8%)	21 (52.5%)	0.95
With cohabitee(s) in own home	17 (41.5%)	15 (37.5%)	
Sheltered Housing	4 (9.8%)	4 (10.0%)	
Care home	0	0	
Home help Visits per week (mean, SD)	17 (41.5%) 2.2 (6.1)	15 (37.5%) 2.5 (6.3)	0.82
District nurse Visits per week (mean, SD)	3 (7.3%) 0.3 (1.4)	3 (7.5%) 0.4 (1.5)	1.00

Table 5:4 Current medications at long-term review of survivors (6 years after study completion)

Drug group	Placebo (n=66)	Pravastatin (n=66)	p
Statin	29 (43.9%)	21 (31.8%)	0.15
Antihypertensive	43 (65.2%)	42 (63.6%)	0.86
Antiplatelet	28 (42.4%)	28 (42.4%)	1.00
Warfarin	5 (7.6%)	2 (3.0%)	0.44
Cognitive enhancer	0 (0.0%)	2 (3.0%)	0.50

Table 5:5 Baseline characteristics of PROSPER survivors who developed significant cognitive impairment compared to survivors who have not

Baseline characteristic	Alive no significant cognitive impairment (n=63)	Alive with significant cognitive impairment (n=28)	p
Age (years)	74 (3)	76 (3.6)	0.007
Gender (male)	29 (46%)	11 (39.3%)	0.55
History of Vascular Disease	30 (47.6%)	16 (57.1%)	0.04
Diabetes	4 (3.2%	2 (7.1%)	1.0
Current Smoker	8 (12.7%)	5 (17.9%)	0.35
Any alcohol intake	35 (55.6%)	12 (42.9%)	0.26
Randomised to Pravastatin	30 (47.6%)	14 (50%)	0.83
Education (years)	15.1 (1.4)	14.8 (1.2)	0.44
SBP (mmHg)	148.7 (20.6)	157.2 (24.7)	0.094
CRP (geometric mean)	2.6 (3.4)	2.1 (3.9)	0.05
IL6 (geometric mean)	2.1 (1.9)	2.0 (1.7)	0.73
D-dimer (geometric mean)	228.8 (1.6)	260.4 (1.7)	0.23

SBP = systolic blood pressure.

CRP = C-reactive protein.

IL6 = Interleukin-6.

Results of continuous variables are mean (SD) except where stated; categorical variables are summarised as number (%). Continuous variables are analysed by 2 sample t-test (using log-transformed data for IL-6 and CRP), and categorical data by Chi-squared or Fisher's exact test as appropriate.

Discussion

We have traced (through the GP) and recontacted a subgroup of 300 Scottish participants of the PROSPER study, at an average of 6yrs 10 months after completion of the randomised controlled trial phase of PROSPER. This time-point is at 10 years after entry to PROSPER and measurement of study baselines. We found approximately 50% of the original study sample are now deceased. This is in line with our pre-study estimates.

We were unable to trace 33/300 (11%) of our study sample. While any loss to follow-up is disappointing this level of case-ascertainment demonstrates that it is possible, using record linkage and GP contact, to ascertain long-term health outcomes for the vast majority (89%) of subjects in PROSPER. The long-term follow-up of the West of Scotland Coronory Preventiont Study (180), another large randomised control trial of statin therapy, was able to obtain details of cardiac morbidity and mortality in 91% of participants.

The GPs were invariably very helpful in responding to our contact. We were able to establish whether survivors had significant cognitive impairment in 91/132 (69%) cases, using a combination of telephone assessment, GP diagnosis, and carer questionnaire. More up-to-date record linkage might reduce loss to follow-up and it may be possible to use record linkage to establish current address

Our previous study experience of telephone contact suggested that it should be possible to gather cognitive data on around 74% of available subjects (173). The acceptance rate in this study for telephone interview was similar to our previous experience at 78/115 (68%). In contrast obtaining contact details for carers /

relatives proved difficult, and this line of enquiry yielded only limited additional information. No other long-term follow-up of a large randomised control trial has attempted to gather data directly from very elderly participants, so we do not have a direct comparison. However it is possible that those that did not participate in the telephone interview were more likely to have cognitive impairment, general poor health and lowere socioeconomic status. We have not been able to study the details of non-participants and this is a potential source of bias.

We found a prevalence of significant cognitive impairment in around 16% of traceable subjects. This is similar to the EURODEM analysis (10) gives the likely prevalence of dementia at age 80-85 of approximately 11% for men and 12.6% for women. We have had to use a pragmatic definition of significant cognitive impairment that included a simple cut-off on the TICSm, although we accept that cognitive impairment is a spectrum and handling the TICSm as a continuous variable may have benefits. However using the TICSm <21 cut-off to diagnose significant cognitive impairment was based on previous evidence (179) but the cut-off is arbitrary and open to criticism. However it is reassuring that our prevalence is similar to the EURODEM analysis. It is possible that we have underestimated the rate of significant cognitive impairment and dementia as the subjects who have been lost to follow-up are perhaps even more likely to have been affected. Additionally the death certificates of those who had died may not represent the true prevalence of dementia.

We were able to define groups of PROSPER survivors with and without significant cognitive impairment. As expected older age and established vascular disease at baseline were risk factors for cognitive impairment. The small number in this

feasibility study restrict what further exploration can be made for risk factors for cognitive impairment; for example it is known that low education is associated with a greater risk of dementia (83;84;181) however we did not demonstrate any such association in our dataset. Education is commonly used as a measure for SES and but using education as a SES measure when considering cognitive impairment is problematic. It is hoped that the role of SES can be explored when the full PROSPER cohort is followed-up but ideally small area statistics will be used as a measure of SES rather then education.

If our results are extrapolated to the whole PROSPER cohort it would be expected that at present 1,260/2,520 (50%) are currently alive; this might be expected to reduce to around 1,000 survivors 1 year after completion of this follow-up study. Of this group of 1,000 survivors it should be possible to determine whether they have dementia in around 750 (75%).

Summary

We found that it was feasible to follow-up elderly survivors from the PROSPER study and the methods could be extended to the whole group. As expected nearly half of the PROSPER participants were dead. Additionally a large proportion of traceable participants had significant cognitive impairment. A large scale follow-up of the PROSPER participants may determine new and novel risk factors for dementia and assess the long-term effect of a period of treatment with pravastatin.

Chapter 6:

Conclusions

Conclusions

Socioeconomic Status and Stroke

Vascular Risk Factors

This thesis aimed to determine if the association between SES and stroke is explained by a greater prevalence of traditional vascular risk factors amongst those of low SES.

A meta-analysis was done to establish if vascular risk factors explain the association between SES and stroke incidence / post-stroke mortality. This demonstrated that the association between low SES and stroke incidence is partly explained by a greater burden of vascular risk factors in those with low SES. This increased prevalence of vascular risk factors explained about 50% of the additional risk of stroke but this meta-analysis could not clarify which vascular risk factor was most critical. Low SES was also associated with increased mortality risk in those who have a stroke although this should be seen as a tentative conclusion as study results were heterogeneous. This link was not explained by increased vascular risk factor burden.

A prospective study of 467 consecutive stroke and TIA patients was undertaken with the aim of establishing whether those with low SES carry higher levels of vascular risk factors. In addition the associations of low SES with stroke severity and access to stroke care services and investigations were studied. This study

demonstrated that smoking is far more common in those of low SES and is likely to be a factor in the association between SES and stroke. However other vascular risk factors, pre-existing vascular disease and general co-morbidity were not more common in TIA / stroke subjects from lower SES groups. This study demonstrated that socioeconomically disadvantaged TIA / stroke patients are younger and have a more severe stroke but appear to have equal access to stroke unit care.

Oral Health

This thesis also aimed to determine if poor oral health contributes to the association between low SES and stroke.

A secondary analysis of a prospective cohort study of 412 stroke patients was conducted with the aim of establishing if poor oral health contributes to the association between SES and stroke and to explore other factors associated with poor oral health after acute stroke. Dry mouth amongst acute stroke patients was very common but there was no association with low SES. There was an association of dry mouth with pre-stroke disability and Urinary Tract Infection and oral *Candida glabrata* colonisation but not dysphagia or pneumonia. There was no association between SES and other measures of oral health. Therefore there was no evidence to support poor oral health as a contributor to the association between low SES and stroke in this study.

Long-Term Follow-up of the PROSPER Study

Vascular disease is a major contributor to cognitive decline and disability in older age. Low SES may play an important role in contributing to vascular cognitive decline and disability. The aim of this study was to assess survival and the feasibility of telephone and postal follow-up of cognition and activities of daily living in a group of 300 elderly participants from the PROSPER study. At 6 years after the end of the study, as expected, nearly half of the PROSPER participants were dead. It was possible to establish the cognitive outcome in 75% of PROSPER study survivors, including 69% who could be contacted and assessed by telephone. A large proportion of traceable survivors had significant cognitive impairment. It is suggested that the methods of follow-up could be extended to the whole group. This research could help to clarify the role of SES in vascular cognitive decline and disability in late life.

Future Directions

Smoking cessation should be made a priority in areas of low SES, in an effort to reduce stroke burden in these high risk populations. However further research is needed to fully clarify the mechanism of association between low SES and stroke incidence. Avenues for exploration might include lifestyle issues including exercise and diet, novel risk factors such as raised homocysteine, and genetic factors.

The vascular contribution to late-life cognitive decline and dementia is potentially modifiable. I have shown feasibility of long-term follow-up and

determination of cognitive and physical function in survivors from an elderly cohort of subjects at risk of vascular disease (the PROSPER study) ; extended use of these methods to the whole cohort may help determine modifiable risk factors for late-life cognitive decline and disability.

Appendices

Appendix A – Data collection sheet for social deprivation and acute stroke prospective cohort study

No.

Demographics/Post Code **Residence** Own/RH/NH

Date collection

Date of admission/clinic visit

Inpatient / Outpatient

If inpatient in Stroke Unit Yes / No

Wheelchair/Bedbound Normally Yes / No

Date and time of symptom onset **Exact** Yes / No*

Arrived within Thrombolysis window Yes/No **Thrombolysis** Yes/No

Symptoms	**- Facial Weakness**	Left / Right / No	
	- Grip	Left / Right / No	
	- Arm Weakness	Left / Right / No	
	- Leg Weakness	Left / Right / No	
	- Speech Disturbance	Yes / No	Expand
	- Visual Disturbance	Yes / No	Expand
	- Sensory Symptoms	Left / Right / No	
	- Neglect	Left / Right / No	
	- Other	Yes / No	
	- Possible to lateralize	Yes / No	
	- Abnormal vascular findings*	Yes / No	
	- Abnormal other findings*	Yes / No	

Duration of symptoms **Admission BM**

Loss of consciousness Yes / No **Syncope** Yes / No

Seizures Yes / No **Headache** Yes / No

History of stroke Yes / No **Type (See Final Diagnosis)**

History of MI/IHD Yes / No **History of clinical PVD** Yes / No

History of revascularisation Yes / No **Family History*** Yes / No / NR

*** SBP, AF, Val HD, No PP** *** Resp, Abdo, or other** ***Parent/Sibling <60 IHD/Stroke**

Total CHOL **HDL CHOL** **ALT**

On lipid lowering drug Yes / No **Hx ↑ Lipids** Yes / No

Admission SBP **DBP**

Later SBP **DBP**

On antihypertensive drug Yes / No **Hx ↑ BP** Yes / No

Pre-existing Diabetes Yes / No Type 1/ Type 2 / No

Admission BG **Diabetes Dx** Yes / No/ Pre-ex

Smoker / Ex / Never /NR **Cigarettes per day**

Waist Circ/BMI **Anitplatelet** Yes / No **Which**

Warfarin Yes/No

CCF	**Dementia***
COPD	**CTD**
Ulcer Disease	**Severe/Mod/Mild Liver Disease**
Diabetes	**Diabetes with end-organ disease**
Severe/Mod/Mild Renal Disease	**Non-met Solid Tumour**
Leukaemia	**Lymphoma or Myeloma**
Metastatic Tumour	**AIDS**
MI	**PVD**
Nil	**Other?**

1st ECG Date **AF** Yes / No **LVH** Yes / No **IHD** Yes / No

CT (MRI) Imaging Date **Haemorrhage / Ischaemia**

Left / Right **Expected / Unexpected**

Carotid Imaging Date **US / MRA / CTA**

Percentage Stenosed L R **Carotid Endarterectomy** Yes / No

Cardioembolic source Date

TTE Yes / No **TOE** Yes / No **TCD** Yes / No

Final Dx Non-stroke TIA POCS LACS PACS TACS MuIn Not known* **L / R**

mNIHSS

Discharge Date **Where Discharged**

Appendix B – Modified National Institute of Health Stroke Score

Item Number	Item Name	Score
1B	Level of consciousness questions	0 = answers both correctly
		1 = answers one correctly
		2 = answers neither correctly
1C	Level of consciousness commands	0 = performs both correctly
		1 = performs one correctly
		2 = performs neither correctly
2	Gaze	0 = normal
		1 = partial gaze palsy
		2 = total gaze palsy
3	Visual Fields	0 = no visual loss
		1 = partial hemianopia
		2 = complete hemianopia
		3 = bilateral hemianopia
5a	Left Arm	0 = no drift
		1 = drift before 10 seconds
		2 = falls before 10 seconds
		3 = no effort against gravity
		4 = no movement
5b	Right Arm	0 = no drift
		1 = drift before 10 seconds
		2 = falls before 10 seconds
		3 = no effort against gravity
		4 = no movement
6a	Left Leg	0 = no drift
		1 = drift before 10 seconds
		2 = falls before 10 seconds
		3 = no effort against gravity
		4 = no movement
6b	Right Leg	0 = no drift
		1 = drift before 10 seconds
		2 = falls before 10 seconds
		3 = no effort against gravity
		4 = no movement
8	Sensory	0 = normal
		1 = abnormal
9	Language	0 = normal
		1 = mild aphasia
		2 = severe aphasia
		3 = mute or global aphasia
11	Neglect	0 = normal
		1 = mild
		2 = severe

Appendix C – Charlson Index as a measure of co-morbidity for use in ischemic stroke outcome studies

Condition	Weight
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Gastro-intestinal ulcer disease	1
Mild liver disease	1
Diabetes	1
Diabetes with end-organ disease	2
Moderate or severe renal disease	2
Non-metastatic solid tumour	2
Leukaemia	2
Lymphoma, multiple myeloma	2
Moderate or severe liver disease	3
Metastatic tumour	6
AIDS	6

Appendix D – Modified Rankin Score

Score	Symptoms
0	No symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

Appendix E – Oxfordshire Community Stroke Project (OCSP) stroke classification

Classification depends on 3 main features –

- Unilateral motor or sensory involvement (face/arm/leg)
- Visual involvement - hemianopia or quadrantanopia or visual neglect
- Higher cerebral dysfunction (dysphasia, dyscalculia, visuospatial disorder/inattention/neglect).

Features	**Classification**
All 3 present or Drowsy & unilateral weakness (visual & higher cerebral involvement assumed)	TACS
2 out of 3 present Isolated speech or visual involvement Motor or sensory involvement affecting one of face/arm/leg	PACS
Motor/Sensory/sensorimotor ≥2 out of face/arm/leg affected Ataxic hemiparesis	LACS
Cerebellar syndrome or brainstem involvement	POCS

Appendix F – Oral assessment guide

Category	Normal/no change 1	Mild to Moderate change 2	Moderate to severe change 3
Voice	Normal	Deeper or raspy	Unable to talk
Swallow	Normal swallow	Some pain on swallow	Unable to swallow
Lips	Smooth, pink and moist	Dry or cracked	Ulcerated or bleeding
Tongue	Pink and moist with papillae	Coated or loss of papillae with shiny and/or redness	Blistered or cracked
Saliva	Watery	Thick or ropey	Absent
Mucous membranes	Pink and moist	Reddened or coated without ulcerations	Ulcerations with or without bleeding
Gingava	Pink and firm	Oedematous	Spontaneous bleeding
Teeth	Clean or no debris	Plaque or debris in localised areas	Generalised

Appendix G– Abbreviated mental test

Question	Score
What is your age?	1
What is the time to the nearest hour?	1
Give the patient an address, and ask him or her to repeat it at the end of the test.	1
What is the year?	1
What is the name of the hospital or number or the residence where the patient is situated?	1
Can the patient recognise two persons (the doctor, nurse, home help etc.)?	1
What is your date of birth? (date and month sufficient)	1
In what year did World War 2 begin?	1
Name the present monarch/prime minister	1
Count backwards from 20 down to 1.	1

Appendix H – Telephone interview for cognitive function (TICSm)

Initials:

Study No:

Assessment Date:

				SCORE
1.	What is today's date? Day/Date/Month/Year/Season	Day Date Month Year Season	1 point 1 point 1 point 1 point 1 point	
2.	What is your age?	Age	1 point	
3.	What is your telephone number including national dialling code?	Tel + code	1 point	
4.	I am going to give you list of ten words. Please listen carefully and try to remember them. When I have finished, please tell me as many as you can remember in any order. Ready?	Cabin Pipe Elephant Chest Silk Theatre Watch Whip Pillow Giant	1 point 1 point 1 point 1 point 1 point 1 point 1 point 1 point 1 point 1 point	
5.	Please take 7 away from 100 Now continue to take 7 away from what you have left over until I ask you to stop.	93 86 79 72 65 58	1 point 1 point 1 point 1 point 1 point 1 point	

6.	What do people usually use to cut paper?	Scissors/shears	1 point	
7.	Please count backwards from 20 to 1	No mistakes	1 point	
8.	What is the prickly green plant found in the desert?	Cactus (only)	1 point	
9.	Please repeat this: “Methodist Episcopal”	Exactly right	1 point	
10.	Who is the reigning monarch now?	Elizabeth, QE, or QE2	1 point	
11.	Who is the prime minister now?	Full name or surname	1 point	
12.	What is the opposite of East?	West (only)	1 point	
13.	Please repeat the list of 10 words I read earlier	Cabin Pipe Elephant Chest Silk Theatre Watch Whip Pillow Giant	1 point 1 point 1 point 1 point 1 point 1 point 1 point 1 point 1 point 1 point	
TOTAL TICS SCORE				

Appendix I – Instrumental activities of daily living

Initials:

Study No:

Assessment Date:

Can you use the telephone?	
Without assistance	2
With assistance	1
Unable	0
Can you get to places out of walking distance?	
Without assistance	2
With assistance	1
Unable	0
Can you go shopping (groceries/clothes)?	
Without assistance	2
With assistance	1
Unable	0
Can you prepare your own meals?	
Without assistance	2
With assistance	1
Unable	0
Can you do your own housework?	
Without assistance	2
With assistance	1
Unable	0

Can you take your own medicine?	
Without assistance	2
With assistance	1
Unable	0
Can you handle your own money?	
Without assistance	2
With assistance	1
Unable	0
TOTAL SCORE	

Appendix J – 20 Point modified Barthel index

Initials:

Study No:

Assessment Date:

Item	Score	Item	Scoring instructions	Score
Bowels	0	Incontinent or needs to be given enema	Rate based on the last week. If needs enema from nurse, then incontinent	
	1	Occasional accident (once/week)	Occasional = once a week	
	2	Continent		
Bladder	0	Incontinent or catheterised and unable to manage	Rate based on the last week	
	1	Occasional accident (max once per 24 hours)	Occasional = less than once a day	
	2	Continent (for over 7 days)	A person with a catheter who can completely manage the catheter alone is scored 'continent'	
Grooming	0	Needs help with personal care	Rate based on the last week.	
	1	Independent face/hair/teeth/shaving	Refers to personal hygiene, doing teeth, fitting false teeth, doing hair, shaving, washing face. Implements can be provided by helper.	
Toilet Use	0	Dependent	With help = can wipe self and do some of the other listed activities	
	1	Needs some help, but can do something alone		
	2	Independent (on and off, dressing, wiping). Should be able to reach toilet/commode, undress sufficiently, clean self, dress and leave		
Feeding	0	Unable		
	1	Needs help cutting, spreading butter etc.	Help = needs food cut, consumer feeds self	
	2	Independent (food provided in reach). Able to eat any normal food (not only soft food). Food cooked and served by others but not cut up		

Transfer (from bed to chair and back)	0 1 2 3	Unable – no sitting balance Major help (one or two people, physical) can sit Minor help (verbal or physical) Independent	Dependent = no sitting balance (unable to sit); two people to lift Major help = one strong/skilled, or two normal people. Can sit up. Minor help = one person easily OR needs any supervision for safety.	
Mobility	0 1 2 3	Immobile Wheelchair independent including corners etc Walks with help of one person (verbal or physical) Independent (but may use any aid e.g. stick)	Refers to mobility about the house or ward, indoors. May use aid. If in wheelchair, must negotiate corners/doors unaided. Help = by one untrained person including supervision/moral support	
Dressing	0 1 2	Dependent Needs help but can do about half unaided Independent (including buttons, zips, laces etc)	Half = help with buttons, zips, etc but can put on some garments alone Independent - Should be able to select and put on all clothes, which may be adapted.	
Stairs	0 1 2	Unable Needs help (verbal, physical, carrying aid) Independent up and down	May carry any walking aid to be independent	
Bathing or Showering	0 1	Dependent Independent (or in shower)	Usually the most difficult activity. Must get in and out unsupervised and wash self. Independent in shower = independent if unsupervised/unaided	
Total score				

Appendix K – Short form of the informant questionnaire on cognitive decline in the elderly (short IQCODE)

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was in 1999. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by circling the appropriate answer.

Compared with 10 years ago how is this person at:

	Much improved	A bit improved	Not much change	A bit worse	Much worse
1. Remembering things about family and friends e.g. occupations, birthdays, addresses	1	2	3	4	5
2. Remembering things that have happened recently	1	2	3	4	5
3. Recalling conversations a few days later	1	2	3	4	5
4. Remembering his/her address and telephone number	1	2	3	4	5
5. Remembering what day and month it is	1	2	3	4	5
6. Remembering where things are usually kept	1	2	3	4	5
7. Remembering where to find things which have been put in a different place from usual	1	2	3	4	5
8. Knowing how to work familiar machines around the house	1	2	3	4	5
9. Learning to use a new gadget or machine around the house	1	2	3	4	5
10. Learning new things in general	1	2	3	4	5

11. Following a story in a book or on TV	1	2	3	4	5
12. Making decisions on everyday matters	1	2	3	4	5
13. Handling money for shopping	1	2	3	4	5
14. Handling financial matters e.g. the pension, dealing with the bank	1	2	3	4	5
15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends	1	2	3	4	5
16. Using his/her intelligence to understand what's going on and to reason things through	1	2	3	4	5

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Modifications to thesis "Cerebrovascular diseases, vascular risk factors and socioeconomic status"

Following the recommendations of internal and external examiners at the oral examination on 7th May 2010, the following changes have been made to the thesis

1. Possible explanations for the association between socioeconomic status (SES) and stroke, other than an increased burden of vascular risk factors, were developed throughout the thesis. These include reduced physical exercise, early life influences and the "inverse care paradox".

2. Throughout the thesis further consideration was given as to how smoking rates could be reduced amongst those of low SES.

3. In chapter 3 more detail was given for the following; how patients were identified; power calculations and the lack of association between co-morbidities and SES.

4. In chapter 4 the methods were expanded. In the discussion more consideration was given to variation in salivary flow and causality of dry mouth and fungal infections.

5. In the chapter 5 discussion further consideration was given as to whether the follow-up rate in participants was good compared to other similar exercises and whether baseline characteristics had influenced this follow-up rate.

6. Grammatical and typographic errors were corrected.