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**THE EFFECT OF CHRONIC LOWER  
RESPIRATORY TRACT DISEASE ON  
SURVIVAL OF PATIENTS  
HOSPITALISED WITH STROKE IN  
SCOTLAND**

Submitted in fulfillment of the requirements for degree of MSc (Med Sci)

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# LIST OF ABBREVIATIONS

## **A**

ACA

Anterior Cerebral Artery

AF

Atrial Fibrillation

AIR

Annual Incidence Rate

ARCOS

Auckland Regional Community Stroke Study

## **B**

BOLD

Burden of Lung Disease

## **C**

CCF

Congestive Cardiac Failure

CI

Cerebral Infarction

COAD

Chronic Obstructive Airways Disease

COLD

Chronic Obstructive Lung Disease

COPD

Chronic Obstructive Pulmonary Disease

CT

Computed Tomography

## **D**

DVT

Deep Venous Thrombosis

## **E**

ECG

Electrocardiogram

## **F**

FEV1

Forced Expiratory Volume in 1 Second

FINMONICA

Finland MONICA Project

## **G**

GCNKSS

Greater Cincinnati/North Kentucky Stroke Study

GOLD

Global Initiative On Chronic Obstructive Lung Disease

GROS

General Register Office for Scotland

## **H**

HR

Hazard Ratio

HRCT

High Resolution CT Scanning

## **I**

IBERPOC

Epidemiological Study of COPD in Spain

ICD

International Classification of Diseases

ICH

Intracerebral Haemorrhage

ICS

Inhaled Corticosteroid

IHD

Ischaemic Heart Disease

ISD

Information & Statistics Division

## **K**

KCSS

Kansas City Stroke Study

KM

Kaplan-Meier

## **L**

LACI

Lacunar Infarct

**M**

MCA

Middle Cerebral Artery

MI

Myocardial Infarction

MONICA

Multinational Monitoring of Determinants and  
Trends in Cardiovascular Disease**O**

OCSP

Oxfordshire Community Stroke Project

OR

Odds Ratio

OXVASC

Oxford Vascular Study

**P**

PACI

Partial Anterior Circulation Infarct

PCA

Posterior Cerebral Artery

PCSS

Perth Community Stroke Study

PE

Pulmonary Embolism

PICH

Primary Intracerebral Haemorrhage

PISCIS

Prognosis of Stroke in Iquique, Chile Study

PNSR

Polish National Stroke Register

POCI

Posterior Circulation Infarct

**R**

RR

Relative Risk

**S**

SAH

Subarachnoid Haemorrhage

SMR

Standardized Mortality Ratio or Scottish  
Morbidity Record

SPSS

Statistics Package for Social Sciences

STROMA

Stroke Register in Malmo

**T**

TACI

Total Anterior Circulation Infarct

TIA

Transient Ischaemic Attack

**U**

UKPDS

United Kingdom Prospective Diabetes Study

**V**

VAsT

Veterans Affairs Stroke Study

VO<sub>2</sub>maxMaximum capacity for oxygen consumption  
by volume (a measure of aerobic capacity  
and cardiovascular) fitness

VTE

Venous Thrombo-embolism

**W**

WHO

World Health Organisation

## **DECLARATION**

The research contained within this thesis was undertaken during my time as a Clinical Research Fellow at the University of Glasgow Department of Cardiovascular and Medical Sciences.

The data used in this thesis was extracted from the Scottish Morbidity Record by James Lewsey. All statistical analyses and other work were performed by me. This thesis in its entirety is my own original work.

I would like to thank James Lewsey in the Department of Public Health for his advice on some of the statistical analysis. I am grateful for Dr Malcolm Shepherd for helping set the goals for this project. I also wish to thank Dr Kate McIntyre and Dr Matthew Walters for making this work possible through their supervision and encouragement.

Special thanks go to Karen Birnie and my parents for being there for me.

## **ABSTRACT**

Stroke is of great medical concern worldwide, being the 6<sup>th</sup> most common cause of adult disability and second leading cause of death. Chronic Obstructive Pulmonary Disease (COPD) is a similarly important cause of mortality and morbidity. The World Health Organisation (WHO) predictions place COPD as the third most common cause of death by the year 2020. There is some pathophysiological overlap between COPD, asthma and bronchiectasis.

Many studies exist which examine stroke incidence and mortality. Fewer studies explore other outcomes or the impact of specific comorbidities on outcomes.

The aim of this thesis is to determine whether COPD, asthma and bronchiectasis have a bearing on the survival of patients hospitalised with their first stroke in Scotland.

157,639 individuals were included in the study, 44.9% of whom were male. 58.1% of all patients had one or more comorbidities and 6.9% had a respiratory comorbidity. 74.1% of all patients survived for 30 days following stroke. 58.1% survived for 1 year and 35.2% for 5 years. The proportions of patients with a comorbid respiratory condition surviving were 71.8% at 30 days, 53.5% at 1 year and 25.9% at 5 years. Median survival for all patients was 818 days. For those with no respiratory comorbidity, median survival was 851 days. For patients with a respiratory condition, median survival was 501 days. Median survival was consistently worse for individuals with a respiratory comorbidity, when further examined by age and deprivation category. The difference in survival was more marked in the younger age groups.

A respiratory comorbidity adversely and significantly affects the outcome, in terms of survival, following first stroke. The reasons for this are not entirely clear and more studies are needed to evaluate this effect further.

# 1. INTRODUCTION

## Stroke

Stroke accounts for the 6<sup>th</sup> most common adult disability<sup>1</sup>, is the second highest cause of death worldwide<sup>2</sup> and the third highest cause of death in the western world<sup>3</sup>. Stroke incidence is estimated to be around 3.4 to 5.2 per 1000<sup>3</sup>. Most studies of stroke epidemiology originate from the developed world although over two thirds of strokes are thought to occur in developing countries<sup>4</sup>. It is estimated that 82 per cent of strokes are infarction, 15 per cent intracerebral haemorrhage and 3 per cent subarachnoid haemorrhage<sup>5</sup>.

## *Pathophysiology & Risk Factors*

Stroke is a disease of cerebral vasculature and can be broadly split into two categories; cerebral ischaemia (the most common), caused by blockage of arteries, or haemorrhage. Stroke results by loss of blood supply to the area of brain supplied by the vessel affected and an inadequacy of collateral circulation. There are several modifiable risk factors for stroke. The main ones are hypertension, cigarette smoking, raised cholesterol, diabetes mellitus and atrial fibrillation<sup>6</sup>.

## Haemorrhage

Primary intracerebral haemorrhage (PICH) occurs mainly as a consequence of hypertensive disease resulting in small aneurysms that rupture. The remainder are due to secondary haemorrhage into an area of infarction, bleeding of vascular malformations or cerebral amyloid angiopathy. Subarachnoid haemorrhages are due to berry aneurysms rupturing into the subarachnoid space<sup>2</sup>.

## Ischaemia

Ischaemia is due to vessel occlusion from either an embolic event or thrombus in atherosclerotic vessels. Various clinical pictures can result depending on the site and extent, but is usually a catastrophic neurological event resulting in a major disability. It can be further classified in several ways, but most commonly by anatomical site of the vessel or by the clinical syndrome produced. The major cerebral arteries are; the anterior cerebral (ACA), middle cerebral (MCA) and posterior cerebral (PCA) supplying the hemispheres with the vertebral and basilar arteries supplying the cerebellum and brainstem.

A widely used clinical classification was devised by the Oxfordshire Community Stroke Project<sup>7</sup>:

- Lacunar infarcts (LACI) are pure motor, pure sensory, sensori-motor stroke or ataxic hemiparesis and are predictive of small lacunar infarcts in the pons or basal ganglia
- Total anterior circulation infarct (TACI) describes higher cerebral dysfunction, a homonymous visual field defect and ipsilateral motor and/or sensory deficit of at least two out of three of the areas of the face, arm and leg. This is usually due to MCA infarction but may involve the ACA
- Partial anterior circulation infarcts (PACI) have only two out of the three criteria from TACI
- Posterior circulation infarcts (POCI) may have ipsilateral cranial nerve palsy plus contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit; disconjugate eye movement; ataxic hemiparesis or homonymous visual field defect alone

These definitions are important in terms of prognosis. 1-year mortalities for each of the syndromes are 60% for TACS, 15-20% for PACS and 10% for LACS<sup>2</sup>. A transient ischaemic attack (TIA) is an ischaemic event similar to any of the stroke events described above, but lasting less than 24 hours.

## ***Diagnosis & Treatment***

Diagnosis hinges on symptoms and clinical signs compatible with stroke followed by confirmatory imaging, usually computed tomography (CT) head scanning. Thrombolysis of strokes is the most important intervention to consider in the acute setting. Based on current evidence, thrombolysis needs to be given within 3 hours of stroke onset for maximum benefit<sup>8</sup>, although there are ongoing trials examining thrombolysis outside this window. The main purpose of CT scanning in the context of thrombolysis is to exclude haemorrhage, where thrombolysis is obviously contraindicated. Due to the narrow timeframe involved and certain criteria that must be met for thrombolysis, the number of patients receiving this treatment is relatively small<sup>9</sup>. Patients with established strokes should be cared for in a specialist stroke unit<sup>10</sup>, where they can receive targeted rehabilitation. Secondary prevention in the form of antiplatelet agents is normally commenced unless there are contraindications (PICH or SAH). If the stroke was embolic due to atrial fibrillation, the patient may be anticoagulated, if suitable<sup>11</sup>. Risk factors such as blood pressure and cholesterol should be controlled and smokers should be strongly encouraged to quit.

# Chronic Lower Respiratory Tract Diseases

## COPD

### *Definition*

Chronic obstructive pulmonary disease (COPD) is sometimes also referred to as chronic obstructive airways or lung disease (COAD or COLD). It is defined by the Global Initiative on COPD (GOLD) as a disease “characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases”<sup>12</sup>. COPD is caused mainly by smoking and is currently the sixth leading cause of death and set to rise to the third leading cause by 2020, according to the World Health Organisation<sup>13</sup>.

### *Pathology*

COPD involves mucociliary dysfunction and structural changes within the large and small airways, blood vessels and pulmonary parenchyma. Excessive mucus secretion is characteristic of chronic bronchitis, part of the spectrum of COPD. The American Thoracic Society defines chronic bronchitis as a cough productive of sputum on most days of at least 3 months of two consecutive years. This may contribute in part to the airways obstruction seen in COPD, with loss of elastic recoil due to emphysema being the main cause. Emphysema, also part of the spectrum of COPD, is a term used to describe the permanent dilatation of terminal air spaces distal to the terminal bronchioles accompanied by destruction of their walls. It may be further described by its distribution within the acinus (the area around a terminal bronchiole) as centriacinar (emphysema close to the bronchiole), panacinar (throughout the whole acinus) or periacinar (distal to the bronchiole). The vascular changes of COPD involve vessel wall thickening due to inflammatory infiltration and increased amounts of smooth muscle and collagen. It is a combination of these various features that are present in different amounts in each individual with COPD.

### *Aetiology*

The most common cause of COPD by far is tobacco smoking. GOLD states that most individuals will have a 20 pack year smoking history (that is 20 cigarettes per day for 20 years). The pathological changes are likely the result of an inflammatory response caused by smoke. Although the damage caused by cigarettes is permanent, stopping smoking will



slow the progression of the disease. Not all COPD is caused by smoking and exposure to passive smoking, wood smoke, other fumes and environmental pollution are thought to contribute. Not all smokers develop COPD implying a degree of genetic susceptibility to the inflammatory damage.  $\alpha$ -1 antitrypsin deficiency is a rare but well-known genetic disorder leading to an increased risk of COPD (even in non-smokers) and there may be others.

### ***Clinical Features and Progression***

Patients usually present with progressing breathlessness, with or without wheeze. Airway obstruction can be quantified by the forced expiratory volume in 1 second (FEV1) and the ratio of FEV1 to vital capacity (VC), which is reduced. The degree of reduction of FEV1 reflects increasing severity. Physical signs vary and correlate poorly to the degree of disease or symptoms. Gas trapping and emphysema cause hyperinflation of the lungs and flattening of the diaphragm (this may be evident on chest X-ray). Skeletal muscle dysfunction and weight loss often occur and are likely caused by chronic inflammation. FEV1 gradually declines, more rapidly in those who continue to smoke and the patients more breathless, resulting in limitation of physical activity. Chronic cough and exacerbations of COPD are common and frequency increases with progression of the disease. Mucus and inflammation within the airways causes a worsening of the airways obstruction leading to an acute deterioration. Eventually, respiratory failure may develop and lead to cor pulmonale. As the patient develops respiratory failure, admission to hospital is usually more and more frequent. Mortality at this stage is extremely high.

### ***Management***

Smoking cessation is essential to slow the progression of disease. Airflow obstruction is largely fixed, so response to bronchodilators is often minimal. There may, however, be a useful symptomatic benefit from even small improvements. A combination of drugs is often used, involving short or long-acting  $\beta$ 2 agonists, anticholinergics and inhaled steroid preparations (which have been shown to reduce the frequency of exacerbations). Oral steroids are usually prescribed as a short course with or without an antibiotic during an exacerbation. Methylxanthines and mucolytics may sometimes be of use. Patients should receive a regular influenza and pneumococcal vaccine. Long-term oxygen therapy is used for patients with chronic hypoxia to reduce cor pulmonale, pulmonary hypertension and polycythaemia. Some patients benefit from procedures such as lung volume reduction surgery or bullectomy. Lung transplantation may be an option depending on suitability.

Pulmonary rehabilitation involving breathing exercises and physical training is of use to reduce breathlessness.

## **Asthma**

### ***Definition***

Asthma comprises chronic airways inflammation, variable (reversible) airway obstruction and hyper responsiveness. There may be a coexisting atopic element, such as rhinitis, but not always. The resulting clinical picture is varied<sup>14</sup>. Some asthmatics, including never-smokers, may progress to a state of fixed airway obstruction similar to COPD. Also, degrees of reversible obstruction may exist in COPD or bronchiectasis<sup>15</sup>.

### ***Pathology***

The airway inflammation central to the disease involves multiple components, involving many cells including eosinophils, mast cells, neutrophils and lymphocytes (CD4+T). There is hypertrophy of smooth muscle and mucous glands plus epithelial damage. Changes in lung vasculature are also known to occur with remodelling and proliferation<sup>16</sup>.

### ***Aetiology***

The cause is still currently unknown and it is likely that there are multiple factors at play. Environmental factors are one possibility. Exposure to cigarette smoke in children, and smoking in adults have both been linked to the development of asthma<sup>17</sup>. Exposure to allergens has also been proposed as a causative factor, but the evidence for this is inconclusive. Similarly, the evidence for environmental pollution causing asthma is also lacking<sup>18</sup>. The influences of diet and breast feeding may also be important, but the interactions are complex and again, the evidence is inconclusive<sup>19:20</sup>.

### ***Clinical Features and Progression***

The disease is quite heterogeneous, but the most common symptoms are cough, shortness of breath, chest tightness and wheeze. The clinical course is usually that of intermittent exacerbations due to infection, allergic stimuli, chemical or occupational exposures<sup>21</sup> with periods of less or no symptoms in between. Some individuals may experience a more chronic course with pervasive wheeze and shortness of breath whilst at the other end of the spectrum; cough may be the only feature. Exacerbations may be severe enough to warrant hospital admission. Extreme cases can lead to the need for invasive ventilation or death – so rapid and careful assessment is important. Obvious difficulty breathing, high pulse rate,

quiet or silent chest on auscultation, confusion or cyanosis are all features of severe life-threatening asthma<sup>22</sup>.

## ***Management***

Treatment of asthma depends on the severity of symptoms and the frequency of exacerbations. Patients with very mild disease and infrequent symptoms may use an inhaled short-acting  $\beta_2$  agonist (such as salbutamol) alone. If symptoms persist, then a low dose inhaled corticosteroid (ICS) is usually prescribed. If the patient continues to have symptoms despite concordance, a long-acting  $\beta_2$  agonist (salmeterol or formoterol) is added, followed by an increase in ICS dose if still uncontrolled<sup>23;24</sup>. A combination inhaler with an ICS is often the most convenient form. The addition of other drugs, for example, leukotriene receptor antagonists or theophylline may be of benefit in selected patients<sup>25</sup>. Smoking cessation should be encouraged and a written asthma management plan should be provided<sup>23;25</sup>.

## **Bronchiectasis**

### ***Pathology***

Bronchiectasis is defined as the permanent dilatation of bronchi. It is usually classified according to radiological appearances<sup>26</sup>. The dilated airways are susceptible to bacterial infection. Secretions may pool in the affected airways and clearance is impaired leading to further colonisation with microorganisms. This leads to cyclical infection, inflammation and further damage<sup>27</sup>.

### ***Aetiology***

Bronchiectasis has many possible causes, perhaps the most widely known being cystic fibrosis. It may arise as a complication after respiratory infections (bacterial pneumonia, viral, fungal or tuberculous infection) in the immunocompetent host or in those with immunodeficiency such as hypogammaglobulinaemia. There are also other congenital causes along with cystic fibrosis, for example primary ciliary dyskinesia or Kartagener's syndrome<sup>26</sup>.

### ***Clinical Features & Diagnosis***

Bronchiectasis usually presents with a chronic productive cough, often with large volumes of thick sputum. Intermittent chest pain and haemoptysis are also fairly frequent. Haemoptysis can result from acute infectious and may rarely be massive due to erosion

into a vessel. Varying degrees of these symptoms may be present, depending on the extent of disease and there may also be features of other pathology such as COPD. High resolution computed tomography (HRCT) scanning is the main imaging method employed to visualise bronchiectasis and assess the site and extent<sup>26;27</sup>. Spirometry is also usually performed as an obstructive picture may result from the small airways inflammation involved. There may also be some reversibility to inhaled bronchodilator therapy<sup>27</sup>.

### **Management**

Breathing exercises and postural drainage to help clear the purulent secretions are widely used, but there is little evidence of benefit<sup>28</sup>. Acute infections should be treated with antibiotics and a sample of sputum cultured. Patients who are chronically colonised, or suffer repeated infections may need long-term courses of antibiotics or aerosolised antibiotic therapy<sup>27</sup>. Some patients may benefit from bronchodilator therapy and inhaled corticosteroids may also be of benefit in reducing inflammation although further evidence is needed. Surgical resection of localised areas of bronchiectasis may be indicated where symptoms are severe<sup>29</sup>.

## **The importance of comorbidities in stroke and possible causative links**

There are many studies of incidence and outcome data regarding stroke but relatively few of these consider the impact of comorbidity on outcome. Even when comorbidities are analysed, respiratory conditions are frequently overlooked. Asthma, COPD and bronchiectasis are relatively common diseases of the respiratory tract with some degree of overlap, particularly in that they are all chronic inflammatory diseases involving remodelling of the lungs. Their impact on the outcome of stroke is largely unknown. For the purpose of this thesis, these three disorders are considered together as “chronic lower respiratory diseases”. As the prevalence of these diseases is increasing, it is important to have an understanding of their relationship with stroke (both in a causative (see below) and a coexisting context) in terms of resource provision and identifying individuals at risk of a poorer outcome so that targeted interventions may be employed.

The inverse relationship between respiratory function and cardiovascular disease has been known for some time and is independent of smoking history<sup>30</sup>. This association has been reproduced in many studies. The independence from smoking history, age and gender continues to be shown in more recent studies. Patients with COPD more often die from

cardiovascular causes than respiratory failure and a greater proportion of hospital admissions are due to a cardiovascular rather than a respiratory cause<sup>31</sup>.

Less is known about poor respiratory function as a risk factor for stroke, but the evidence is growing. Kurl et al, using VO<sub>2</sub>max (maximum consumption of oxygen) as a measure of cardio-respiratory fitness, found a relative risk for stroke of 3.2 for those with a VO<sub>2</sub>max of <25.2mL/kg per minute compared with VO<sub>2</sub>max >35.3mL/kg per minute<sup>32</sup>. The Renfrew and Paisley prospective population study looked at all mortality outcomes relative to FEV<sub>1</sub> after adjusting for age, smoking history, diastolic blood pressure, cholesterol, body mass index and social class<sup>33</sup>. Individuals with an FEV<sub>1</sub> in the lowest fifth (<73% predicted) had a relative hazard ratio of 1.65 for stroke mortality, with a gradient of decreasing risk with a higher FEV<sub>1</sub>. The Copenhagen City Heart Study showed a 30% increased risk in the lowest FEV<sub>1</sub> group when compared to the group with highest FEV<sub>1</sub><sup>34</sup>. The association was strong for both first incident and fatal first stroke (death within 28 days). This relationship between FEV<sub>1</sub> and stroke has been shown in several other studies<sup>35;36</sup>.

Vascular complications might be expected in individuals with reduced lung function related to smoking, such as COPD, but there is no satisfactory unifying explanation for the results corrected for smoking or demonstrated in never-smokers. Although smoking no doubt contributes to this risk, other mechanisms must be involved. There are several theories to explain why poor lung function may be a chronic risk factor for stroke, or may act by contributing to acute triggers for stroke.

It is still not entirely clear why there is an increased vascular risk in poor lung function, over and above that expected from smoking or in never smokers. Systemic inflammation seems the most attractive way of explaining how individuals with a primarily respiratory condition suffer an excess of cerebrovascular morbidity and mortality. Higher levels of inflammatory markers are found in subjects with poor lung function<sup>37;38</sup> and inflammation is integral to atherosclerosis<sup>39</sup>. Its merit is in also providing a link to other explanations. Infection is associated with an increase risk of stroke<sup>40;41</sup> and influenza vaccination may well be protective<sup>42</sup>. There is evidence that oxidative stress occurs systemically in COPD<sup>43</sup> and may play a large part in atherosclerosis<sup>44</sup>. Both infection and oxidative stress would interact with inflammation. Further research into this area may yield an increased understanding of the way inflammatory conditions affect the blood vessels and may offer novel therapeutic avenues or screening tools for both respiratory and vascular medicine.

## **2. LITERATURE REVIEW**

### ***Aims***

The aim of this review is to evaluate current literature on stroke incidence, comorbidities, mortalities and temporal trends with specific reference to chronic lower respiratory tract diseases, where possible.

### ***Method***

OVID Medline searches were undertaken using keywords “stroke”, “comorbid”, “mortality”, “incidence”, “epidemiology” and other relevant headings. Lateral referencing of the literature from the papers obtained initially was used to increase the yield of pertinent studies.

### ***Studies of Stroke Epidemiology***

There is a large amount of published data from the last few decades describing stroke epidemiology. There are papers from all over the globe, but the bulk of these originate in Western Europe or the United States. This makes global estimates of stroke epidemiology difficult as most of these studies describe developed countries where, according to WHO estimates, only a third of global strokes occur<sup>4</sup>. Study sizes vary from less than 100 to tens of thousands and often have differences in data collection, subject inclusion and presentation of results. These differences can range from quite subtle to much bigger. It is these differences that make direct comparison of the available data troublesome or not very valid. Warlow and Sudlow<sup>45</sup> suggested a set of criteria regarding stroke incidence study design. They also concluded that very few are easily comparable and there was a lack of data meeting their ideal criteria covering developing countries. Ignoring the differences to an extent, the studies can be broadly placed into three groups; prospective population-based studies (OXVASC or Framingham), stroke registers (Finland) and hospital-based or discharge data studies (Quebec). The more comparable studies are the prospective population-based studies with multiple overlapping sources of case ascertainment. 80% of cases should be diagnostically confirmed by CT scanning with “hot pursuit” and follow-up of cases<sup>46</sup>.

## **Stroke Incidence**

The literature reviewed quote similar incidence rates for stroke. This is unsurprising given that they mostly cover similar populations in terms of geography and likely ethnicity. The prospective studies reviewed report incidence of stroke ranging from 94.1 – 227 per 100,000 person years. Stroke registers report between 85.45 and 235 per 100,000 person years. The lower rates were seen in Chile, Brazil and Western European studies with higher rates seen in Japan, Sweden, Finland and Italy. As stated earlier, differences in study design make determining whether these are real or artifact very difficult. It is also important to consider that the studies cover differing time periods. One problem highlighted by Warlow and Sudlow can be seen in the Minneapolis study, reporting a rate of 416.8 per 100,000 person years in 1980. This was a study of hospital discharge data and did not strictly include first incident strokes. It captured one stroke per person per year meaning that some strokes may have been an individual's second or later stroke if an earlier stroke was prior to the study period. This may be responsible for such a high figure. Another factor to consider is the population to which the figures are standardised. The PISCIS<sup>47</sup> study in Chile had one of the lower rates at 97.4 per 100,000 person years. This was possibly due to case ascertainment in that strict methods to ensure non-hospitalised cases were captured were not employed. The authors also present the incidence as 94.1 or 140.1 when adjusted to World or European populations – the latter figure appearing more in line with the European stroke studies. It is likely important that the mean ages in PISCIS (61.2 in men and 68.5 in women) were considerably lower than other studies (especially for males). It is well known that stroke incidence increases with age<sup>48</sup>, therefore a younger population may have a lower stroke incidence if people are dying of other non-stroke causes when compared to populations such as Western Europe where the mean age has increased over the last century. The Rotterdam study<sup>49</sup> returned rates of 1.7 per 1000 person years for men aged 55-59 and rising to 69.8 in those aged over 95. A similar trend was seen in Oxfordshire Community Stroke Project<sup>50</sup> (OCSP), although presented by stroke subtype. For instance cerebral infarction occurred at a rate of 0.1 per 1000 per year at age less than 45 and 15.0 in those over 85. In Auckland, Bonita *et al*<sup>51</sup> demonstrated rates of 118 per 100000 at ages 45 to 54 and 2422 per 100000 over the age of 85.

Although many of the papers do present the data in crude form and adjusted to European population, this is not always the case. They may be adjusted to local population, world population or others. The Poznan<sup>52</sup> incidence was adjusted to the US population of 1960 which limits its comparability to other European studies. The higher incidence rates in

developing countries, Eastern Europe and the Nordic countries may be due to levels of deprivation, nutrition, pollution, lifestyle and primary prevention availability<sup>53</sup>. Finland was known to have very high levels of cardiovascular risk factors in the seventies<sup>54</sup>. The higher rates seen in Japan (which should be comparable with other developed countries) may be due to other genetic or environmental factors<sup>3</sup>.

Nearly all the studies reviewed present sex-specific data also. Almost universally, age-adjusted incidence of first stroke is higher in men than in women. Notable exceptions to this are the Kolkata study in India (178.01 and 117.01 per 100,000 person years in women and men respectively – age and sex standardised rates) and the Sicily study (185 and 123 per 100,000 person years in women and men respectively – standardised to European population). The male to female ratio of the Kolkata study was roughly equal to the census population of the city and distribution of the study population by age range was also comparable between sexes. The authors felt the high incidence in women was real and reflected the high prevalence of hypertension in Indian women. The sex ratio in the Sicily study was very heavily weighted towards a female population, only 41.9% of the sample was male. This has also likely weighted the results towards females. The authors do not comment on this difference but are aware of the limitations of such a small sample size (62 confirmed, first-ever strokes).

### ***Temporal Trends in Stroke Incidence***

Many of the studies reviewed can give some idea of changes in stroke incidence over time and most conclude that there has been a reduction in incidence. The Perth Community Stroke Study (PCSS)<sup>55</sup> reported a large change, greater in men than in women. There was a decline of 25% from 1990 to 1996 and a 43% reduction in rates from 1996 to 2001. The authors found that this 5.5% annual decrease corresponded to a significant parallel reduction in stroke risk factors over both study periods. The Quebec study reported a reduction in ischaemic strokes of 32.5% in men and 25.5% in women for the last five years of the study. However, there was a small increase seen in the youngest age group (< 55 years) and a small increase in haemorrhagic strokes for both sexes. The authors believe that the reason for this may lie in the increased availability and accuracy of diagnostic imaging in stroke, such as CT scanning, the increasing prevalence of cerebral amyloid angiopathy or the increased use of antithrombotics as primary and secondary prevention. The Minneapolis study of stroke hospitalisation found the rate to be stable through the study period, although the problems of interpreting this study have been previously



discussed. Dijon similarly saw a stable incidence rate despite an increase in the total number of strokes and an ageing population. The authors gave the possible explanations of failure to control hypertension and the rising incidence of diabetes. The three Finnish studies confirm a decline in stroke incidence, felt to be due to a national effort to lower risk factors which began as the North Karelia Project in the seventies<sup>54</sup>. Two Swedish studies in Malmö<sup>56</sup> and Lund-Orup<sup>57;58</sup> did not share a decrease in stroke incidence with their Nordic neighbour Finland. Both studies revealed an increase between the 1980s and 1990s. This trend was not continued in the 2001/2 data from Lund-Orup and it was thought that, at least in part, differences between the method of data capture in the two periods were responsible for this trend. Malmö saw an annual increase of 3.2% in men and 2.9% in women. The authors of both the Malmö and Lund-Orup studies postulated that a lack of adequate treatment of or an increase in risk factors, particularly hypertension and obesity, or a change in the ethnic diversity of the Swedish population over the study period may help explain the findings. Pessah-Rasmussen et al found no evidence that increased stroke incidence was due to decreased mortality from myocardial infarction in the Malmö data, but Johansson et al thought that an increase in survivors of ischaemic heart disease may be a factor. A review of population studies in China<sup>59</sup> found stroke incidence to be unchanged overall, but there were several studies showing an increase. Male and female rates were seen to increase in eight of the twelve populations with female and male rates decreasing in four and three populations respectively. The authors were not certain of the reason for this but did conclude that none of the studies met criteria for comparability as suggested by Sudlow and Warlow so flaws in the data could not be discounted.

### ***Baseline Characteristics - Age & Sex***

As with stroke incidence, the studies reviewed tend to correlate well regarding the baseline characteristics of the study population. Again, this is largely unsurprising given that most of the data covers predominantly white European populations. The studies with substantially more women being Rochester<sup>60</sup> at 41% male and the Sicilian study at 41.9% male. At the other end of the spectrum the highest male proportions were seen in Kolkata (55% male), PISCIS (56%), Lund-Orup (56.1%), STROMA (54.4%) and FINMONICA<sup>61</sup> (56.5%).

The studies have similar mean or median ages and show the same tendency for men to be several years younger at the time of their first stroke. The youngest ages are seen in Brazil (mean 65.1 men, 65.3 women), PISCIS (mean 61.2 men, 68.5 women), Kentucky (mean 61 both sexes) and the Finland study of 1971-73 (mean 61.9 men, 65.2 women). This may

be due to the presence of unfavourable risk factors in the population and it is worth noting that the mean age in the Finland 1989-91 study rose (67.7 men, 74.6 women) as stroke incidence fell, presumably with the national strategies to reduce cardiovascular risk and hence improved survival. The low age in the South American studies may reflect a younger population on the whole due to poorer survival from all causes of mortality with advancing age.

### ***Comorbid Diagnoses***

There is little data available regarding the comorbidities present in the study populations at the time of stroke. Where the data does exist, it predominantly covers the well-known associations; hypertension, diabetes mellitus and ischaemic heart disease. Fewer studies have recorded the presence of congestive heart failure and chronic respiratory diseases such as COPD. Not all of the studies are strictly of first incident strokes and several present an analysis of a subtype of stroke only. The studies also use different definitions for the comorbidities which are also sometimes self-reported, calling into question the accuracy. These factors make direct comparisons of the results difficult.

### **COPD/Chronic lower respiratory diseases**

COPD is the least frequently measured comorbidity, appearing in only five of the studies reviewed. There is no data to see how the prevalence has changed over time, nor is there sex-specific data. The stroke register of Sagrat Cor-L'Allianza Hospital, Barcelona recorded it as present in 5.8% of patients from the data up to 1995<sup>62</sup> and in 6.8% up to 1997<sup>63</sup>. The data was concerned only with ischaemic stroke subtypes and the later study was of patients over 85 years although data for all ages was presented. This figure is a little lower than the prevalence of COPD in Spain (9.1%) as recorded by the IBERPOC multicentre epidemiological study in 2000<sup>64</sup>. Little can be inferred from this as comparing and estimating prevalence for COPD is especially difficult. Definitions relating to FEV<sub>1</sub> differ and it is likely under diagnosed in many parts of the world. The American studies VAS<sub>t</sub> (Veterans Affairs Stroke Study) in North Carolina and KCSS (Kansas City Stroke Study) report rates of 15.3% and 14% respectively. The data from BOLD (Burden of Lung Disease)<sup>65</sup> estimates a prevalence of COPD in the United States of 2-5% based on Spirometry but 5-15% based on symptoms. KCSS used self reported comorbidity, whereas VAS<sub>t</sub> used hospital discharge coding. In either case, the use of FEV<sub>1</sub> to confirm the diagnosis is likely to be low, which may account for these studies being closer to the symptom-based figure from BOLD. A small study of consecutive stroke admissions to Glasgow Royal Infirmary<sup>66</sup> found a COPD prevalence of 10.2%. The authors did not

comment on how COPD (or other risk factors) was defined other than being identified in the past medical history. The prevalence in the Scottish population is currently 1.8%<sup>67</sup>. Although it may be due to differences in definitions, the high prevalence of COPD seen in the Scottish and American studies when compared to the whole population could be real. As discussed previously in this thesis, COPD is becoming recognised as a risk factor for vascular diseases and a risk factor for stroke would be expected to be more prevalent in the study population.

### **Ischaemic Heart Disease (IHD)**

The lowest rates of IHD are seen in ARCOS<sup>68</sup> (Auckland Regional Community Stroke Study) and OCSP/OXVASC<sup>69</sup>. In both these studies, the prevalence of IHD was relatively stable. In 1981 ARCOS had a rate of 10.9% and 12% in 2003. OXVASC had a small reduction in IHD; 15.6% in 1981 and 12.2% in 2004. OXVASC also saw a (larger) reduction in patients with a previous myocardial infarction (MI) from 18.2% in 1981 to 12.6% in 2004. The mean age of the study population did not change in either study. OXVASC saw a statistically significant increase in treatment of hypertension and antiplatelet use, plus a decrease in smoking over the study period. This is a likely explanation for the decrease in IHD, MI and stroke incidence. ARCOS saw similar reduction in smoking prevalence but a smaller increase in treatment of hypertension. It may be that under treatment of hypertension is a factor in the modest increase in IHD seen, or it may be that improvements in treatment led to less severe strokes. Indeed, survival rates post-stroke improved in ARCOS. It may be that an increase in survivors of stroke has led to an increase in the prevalence of IHD. The highest rates of IHD were seen in Perth (34.7%)<sup>55</sup>, Glasgow (35.4%)<sup>66</sup>, Sicily (29%)<sup>70</sup>, Poland (Polish National Stroke Register - PNSR) (24.6-42.4%)<sup>71</sup> and several of the American studies. Given that stroke and heart disease share risk factors, it is unsurprising that many of the studies show a high prevalence and that higher rates are seen in populations with higher stroke incidence.

### **Atrial Fibrillation (AF)**

The lowest rates of AF were seen in Framingham at 1-2% in the 1950-1977 period and 3-5% in 1990-2004. This is significantly lower than figures from other American studies (5-33% in Rochester<sup>60</sup> and 11-16% in Portland<sup>72</sup>, although Portland chose those aged over 65 only). A possible reason for this is that the Framingham cohort was composed of initially healthy volunteers and therefore not directly comparable with the prospective Rochester

study or the Portland study which used retrospective hospital data. The current estimated prevalence of AF in the general American population is 0.95% (rising to 9.0% in the over eighty age group)<sup>73</sup>. A European study in Rotterdam<sup>74</sup> found similar results to American figures with an overall prevalence of 5.5% in the general population and 17.5% over 85 years. The highest rates within stroke study populations were reported in the PNSR (10.7% for haemorrhage, 23.1% for ischaemic stroke & 30.8 for undefined stroke), Barcelona (27% in 1995 and 29.6% in 1997 and Dijon (22.9% in the eighties, 29% in the nineties and 23.1% in 2000-2004). The other studies give rates between 10% and 20%. Rates in OCS/OXVASC rose from 9.6% at the start of the study to 16.8% in the period 2002-04. Whether this is a real increase is not clear, but it is worth remembering that the incidence of stroke fell over this period. There may have been an increased vigilance for AF over the period or an increased pickup of an already prevalent condition. With improvements in technology and ease of recording electrocardiograms (ECG), which are now available in some general practices, it is possible that this is the explanation. A further study in Rochester<sup>75</sup>, specifically examining AF in incident strokes also saw an increase. The prevalence of AF in cases of incident stroke was measured in the periods 1960-69, 1970-79 and 1980-89. It was found to be 11%, 17% and 22% respectively. There was a doubling of odds of AF for each decade of life. The authors thought that the increase in prevalence over time could not be explained by increased use of ECGs. Although there was an increase over the first study decade, there was no further significant increase over the second or third decades. They found an increase in all risk factors in the subjects, many of these comorbidities also being risk factors for AF (hypertension and valvular heart disease in particular) and felt this was the reason for the rise in AF prevalence.

### **Congestive Cardiac Failure (CCF)**

It has been known for several decades that heart failure is a risk factor for stroke<sup>76</sup> and shares several risk factors, so its prevalence within stroke patients should not be surprising. The lowest comorbidity rates were seen in PISCIS, Chile (4%)<sup>47</sup>, Barcelona (5.7%)<sup>62;63</sup> and Kansas (6%)<sup>77</sup>. The highest rates were recorded in the Portland study (16% in 1967-71 and 20% in 1981-84)<sup>72</sup>. The remainder of the studies reviewed found rates between these values. Again, differences in study design make comparisons difficult. The 1999 National Health Interview Survey in the United States<sup>78</sup> estimated the prevalence of CCF in the general population (by age group) to be 0.1% (18-39 years), 1.1% (40-64 years), 3.6% (65-74 years) and 5.5% (75-105 years). This was self-reported data and may represent an

underestimate. The figures from the American stroke studies are a little higher; 8.7% from Rochester<sup>60</sup> (with a mean age between 67 and 80 and much higher in Portland. Given the links between CCF and stroke, it may be expected that the prevalence of CCF should be higher in a stroke population. The significantly higher figures from Portland could possibly be due to a difference in study design. Rochester was prospective, population-based whereas Portland chiefly used hospital data with some community sampling and included only subjects over 65 years old. The prevalence in a principally hospital-based sample may be higher. It is difficult to determine the cause for the apparent increase in CCF prevalence from 1967-1984 in the Portland study. The Quebec study showed no change from 1988-2002 and a study in Minnesota<sup>79</sup> (in the general population) also showed no change from 1979-2000. Portland may have been seeing an increase in prevalence due to better diagnosis (improvements in cardiac ultrasonography) or an ageing population with increasing comorbidity.

## **Diabetes Mellitus**

Diabetes Mellitus is also a well-known vascular risk factor with a two-fold increase in the risk of stroke within the first five years of diagnosis when compared to non-diabetics<sup>80</sup>. In light of this, a high prevalence within a stroke population would be expected. Interestingly, the United Kingdom Prospective Diabetes Study (UKPDS) discovered that it was treatment of co-existing risk factors (chiefly hypertension) in diabetes that would lower an individual's risk of stroke<sup>81</sup>. Having a lower fasting plasma glucose led to a reduced risk of most adverse outcomes in diabetes, but not stroke<sup>82</sup>. The lower rates were recorded in Auckland<sup>83</sup> (ARCOS; 9% in 1981-82, 15.9% in 2002-03), Perth<sup>55</sup> (PCSS; 12% in 1989-90, 19.1% in 2000-01), OCSP & OXVASC<sup>69</sup> (10.5% in 1981-84, 9.5% in 2002-04), Framingham<sup>84</sup> (5-7% in 1950-77, 9-12% in 1990-2004). The highest rates were seen in Carolina (VAST<sup>85</sup>; 36% in 1995-97, 29% in 1979-80 and 17% in 1970-73<sup>86</sup>), Sicily<sup>70</sup> (26%), Kansas (KCSS<sup>77</sup>; 23%), Barcelona<sup>62;63</sup> (20% in 1995, 21.4% in 1997), Chile (PISCIS<sup>47</sup>; 21%), Poland<sup>71</sup> (PNSR; 12.7% for ICH, 21.2% for ischaemic stroke and 20.5% for unclassified strokes). Despite having lower prevalence of diabetes at the start of the studies, Framingham, Perth and Auckland all saw a rise throughout the period. This trend was also seen in Dijon<sup>87</sup> (10.4% in 1985 to 17.5% in 2004), Quebec<sup>88</sup> (11-21% in 1998 and 19-27% in 2002) and North Carolina. Prevalence is known to increase with age, has been increasing over time and is expected to continue increasing as global obesity levels rise<sup>89</sup>. These studies fit with this observation. Definitions of diabetes and clinical vigilance have

changed over the past few decades and there may be more people being diagnosed with diabetes that would have gone unnoticed in the past. Despite this, it is likely that the increases seen are real given the global evidence on rising obesity and diabetes levels. The high levels in the North American studies also fit with the fact that North America as of the year 2000 had the third highest level of diabetes in the world behind India and China<sup>89</sup>. Italy was ranked ninth on this table. OXVASC found the prevalence of diabetes to be stable, which is consistent with UK data over the same period (2.1% in 1995 and 2000)<sup>90</sup>. However, more recent data suggests there has been a sharp rise in the prevalence of diabetes in the UK<sup>91</sup>, with as much as a 50% increase in the past decade.

## Hypertension

Hypertension is the most potent risk factor for all types of stroke<sup>92</sup>, this having been demonstrated in the Framingham study<sup>93;94</sup>. With this knowledge, it would seem very likely to find a high prevalence within the stroke population. This is indeed borne out, with almost all of the studies having a prevalence of over 50%. The lowest rates are seen in the Portland study (24% in 1967-71, rising to 56% in 1981-84), Quebec (35-38% in 1988 and 51-56% in 2002), Kentucky (GCNKSS<sup>95</sup>; 44% in 1993-94 and 45% in 1999) and Framingham (48-56% in 1950-77 and 30-34% in 1990-2004). A much higher value (72.9%) was seen in the Rochester study<sup>60</sup>. Framingham and Kentucky may be artificially low for similar reasons. Framingham was a cohort of initially healthy volunteers and the Kentucky study took its comorbidity data from the whole study population including both stroke and non-stroke individuals. Very high prevalence is also seen in Poland (72.1% for ICH, 61.8% for ischaemic stroke and 64.3% for unclassified strokes) and Buenos Aires<sup>96</sup> (77.1% all ages and 82.7% in the over 80s age group). South America and Eastern Europe are known to have unfavourable cardiovascular risk profiles. The prevalence, although still high, was a little lower in the Western European Studies; Dijon with 65.3% in 1985 and 64.1% in 2004, Barcelona with 53.2%, Glasgow with 55.1% and OXVASC with 60.9% in 1981 and 45.7% in 2004. Although Dijon saw no change in premorbid hypertensive history, there was a significant decrease in diastolic hypertension at stroke onset (53.7% in 1985 to 36.4% in 2004) with a parallel fall in smoking rates and mortality. In essence, this likely reflects an increase in more aggressive treatment of hypertension as was observed in a French study of trends in hypertension over the same time period<sup>97</sup>. OXVASC saw a significant reduction in the premorbid systolic and diastolic blood pressure values with an increase in preventative medication (antihypertensives, antiplatelet and cholesterol-lowering) and decrease in smoking. This again was felt to reflect better recognition and treatment of vascular risk and is a similar finding to Dijon, although

recorded data are not entirely comparable. Unlike Dijon, OXVASC did not record the prevalence of premorbid hypertension but the number of blood pressure measurements above target at presentation and the prevalence of treated hypertension. Therefore, although we can say that treatment increased and systolic and diastolic values responded favourably, the prevalence of hypertension (whether treated, partially treated or untreated) may have remained static or increased over the study period.

### **Stroke Mortality**

As with reporting of incidence and comorbidities, there are large differences in the reported case fatality or survival rates. This may well be due to the large differences in study design employed but may also be due to other factors such as changes in incidence or health care.

### **30-Day and 1-Year Mortality**

The reported 30-day survival rates follow trends in stroke incidence. Higher survival rates are seen in studies from the Western world (especially American and UK-based studies). The lowest US figure (for all stroke types) was 67% in Portland<sup>72</sup> (1967-1971) and the highest 95% in North Carolina<sup>86</sup> (1979-1980). A similarly high rate of 90.7% (females) and 90% (males) was seen in the Swedish Malmao<sup>56</sup> study. Lower survival rates were seen in the Finish Numminen study<sup>98</sup> at 65.2%. As discussed earlier, this likely reflects the high incidence of cardiovascular risk factors that was known to be present in Finland during this time period. The lowest reported 30-day survival rates occur in the Moscow<sup>99</sup> (63%) and Kolkatta<sup>100</sup> (59.92%) studies. Das and colleagues thought the high fatality rate in Kolkata likely reflected a lack of good quality medical care. Schmidt *et al* offer no explanation as to the high mortality rate in Moscow. Their analysis of the comorbidities present show high levels of diabetes, obesity, kidney disease and seizures. A possible explanation is that this directly influenced either the severity of stroke or immediate complications. Despite the differences seen in 30-day survival rates, 1-year rates are surprisingly similar. Numminen reports Finish figures as 56.6%-65.9% through the time period. The Oxfordshire study reported (by subtype) between 16% and 77%, Howard (North Carolina) demonstrated 49% to 62% over 1970-1980 and Barker (Portland) showed 47% to 64% (1967-1985). Schmidt in the Moscow study returned a rate of 48%. Although it is difficult to draw specific conclusions from data that is not directly, this may be partly due to a survivor effect. Countries with lower 30-day survival may represent people with a worse risk factor or comorbidity profile presenting with more severe strokes. The survivors are

therefore “selected” to be healthier individuals and have similar 1-year mortality to other countries that had more favourable 30-day mortality.

## **Survival in Stroke Subtypes**

One of the earlier stroke studies was performed in Rochester<sup>101</sup> from 1955-1969. This showed a survival rate of 72% at 30 days for all strokes and revealed a trend in stroke subtypes that has been reproduced many times since. The 30 day survival rate for subarachnoid haemorrhage (SAH) was 48% and for intracranial haemorrhage (ICH) was only 16% compared to a rate of 81% for thrombosis or embolic strokes. This rather dismal outlook for SAH is repeated in studies from before 1980. Framingham<sup>102</sup> found a rate of 18% for ICH and 54% for SAH, the North Carolina study<sup>86</sup> demonstrated a rate of 32% for ICH. There were higher survival rates seen in the Finland study 1972-1973<sup>98</sup> at 59.5% for SAH and 26.8% for ICH. ICH due to haemorrhagic transformation is known to be associated with larger infarcts. This can lead to a rise in intracranial pressure and a poorer outcome<sup>103;104</sup>. Although it could be that haemorrhagic strokes are more severe and more immediately life threatening, Bamford *et al*<sup>105</sup> state that stroke as a result of haemorrhage is also more likely to show dense neurological signs. This could lead to a bias in that these patients are more likely to be admitted to hospital and are over-represented in some of the studies. These factors of course depend on the design of each individual study, but it is clear that all the studies agree that haemorrhagic strokes convey a poor immediate and long term prognosis that is likely real. The authors of most studies agreed on the reasons behind high case fatalities amongst unspecified strokes. A confirmed diagnosis in a clinically suspected stroke is less likely to be pursued when felt inappropriate in a moribund patient.

## **Temporal Trends in Stroke Mortality**

In general, studies from more recent years show an improvement in survival rates from earlier studies (i.e. those from the 1950s to the 1970s), the obvious exception being the Kolkata study. In his review of stroke, Donnan<sup>2</sup> believes this is most probably due to four main advances in healthcare; aspirin, acute stroke units, thrombolysis and surgical decompression of intracerebral oedema. Barker *et al*<sup>72</sup> found an increase in 30-day survival from 67% (1967) to 82% (1985). They attributed this to a decrease in severity of strokes (more specifically, a decrease in the number of cases presenting with coma) and a decrease in hypertensive heart disease amongst the population. Howard *et al*<sup>86</sup> had similar findings and conclusions in the North Carolina study. The Finland studies by



Numminen<sup>98</sup> also saw an improved survival rate over the study period. As discussed earlier, there was a national drive to reduce adverse cardiovascular risk in Finland in the seventies. Numminen also felt improved survival was due to decreased severity of stroke<sup>106</sup> (there was a reduction in the proportion of ICH), which in turn may be due to this effort to reduce risk factors. Bonita *et al*<sup>51</sup> also saw evidence for a reduction in severity of stroke in Auckland. The PCSS<sup>55</sup> saw no significant increase in survival (78.1% in 1989 and 79.8% in 2001). There were other changes in the population, however. The median age increased with a greater proportion of over 65s and the overall incidence of stroke fell. There was also an increase in premorbid diabetes and it may be that this coupled with an older stroke population led to stable mortality despite a falling incidence. In both the Malmö<sup>56</sup> and Oyabe<sup>107</sup> studies, a fall in mortality was seen that was greater for women than for men. Neither study could determine whether this represented changes in medical care or changes in stroke severity.

## **Cause of Death**

In the OCSF, Bamford *et al*<sup>105</sup> demonstrated that 53% of deaths within 30 days occurred from neurological consequences of stroke and within 72 hours of admission in over half of the cases. This was most common in haemorrhagic strokes, whereas in ischaemic strokes 51% of deaths were due to pneumonias and pulmonary emboli. Similar figures were arrived at in the Moscow study by Schmidt and colleagues<sup>99</sup>. In the acute period, 55.4% of deaths were due directly to the brain lesion. The remaining deaths were due to pneumonia (17.6%), pulmonary embolism (13.6%), heart failure (8.6%) and MI (2.9%). After the first 3 months and for the 7 years of follow up, recurrent stroke as a cause of death remained at a fairly constant level; 24.8% at the start and 19.4% at the end. Pneumonia was more common earlier on (20.0% after the first 3 months) but reduced to 13.4% of deaths by 7 years. The biggest shift was seen in heart failure and MI – accounting for 25.7% of deaths at 3 months but rising to 50.8% by the 7 year mark. Vernino *et al*<sup>108</sup> also found that the stroke itself was primarily responsible for death in around 50% of cases up to 30 days. From 31-365 days, pulmonary and cardiac causes were prominent each causing approximately 30% of deaths each. This suggests that management of cardiovascular risk post stroke is very important. The Danish MONICA study<sup>109</sup> found that 67.5% of patients with nonfatal stroke (those surviving over 27 days) went on to die of cardiovascular causes. The standardized mortality ratio (SMR) for post-stroke cardiovascular death was calculated to be four times greater than the general population. SMR for stroke death in this period was 8-9 times greater than the background population although the authors postulated that

this may be an over-representation. Physicians may be more likely to record stroke as a cause of death in a stroke patient when a more accurate cause of death may not be immediately obvious. PISCIS<sup>47</sup> provides data on cause of death both less than and after 30 days from stroke onset. Less than 30 days, the main cause of death (63% of these deaths) by far is neurological sequelae of stroke. Pneumonia accounts for 21%, sepsis 4% and cardiac 3%. After 30 days, cardiac deaths account for 23%, pneumonia 20%, sepsis 8% but 31% were recorded as “unknown” (where there was insufficient data to draw a conclusion). In simpler terms, immediate deaths are due to the stroke itself and deaths in the 30 day survivors are due to consequences of immobility or cardiac causes. It is for this reason that immediate care is focused on limiting neurological damage (thrombolysis or treatment of oedema). Later care must focus on reducing the effects of immobility or aspiration (physiotherapy, heparin or compression stockings and speech and language therapy) and secondary prevention (aspirin).

### **Factors Influencing Mortality**

Howard *et al*<sup>86</sup> demonstrated that unconsciousness was the strongest predictor of death with a hazard ratio (HR) of 3.04. Diabetes had a HR of 1.28 and cardiac disease a HR of 1.92 in the haemorrhage subgroup. In the Portland<sup>72</sup> study again, coma was found to be the major predictor of death (1-month HR of 7.74 and 1-year HR of 5.61) with a history of MI of hypertensive heart disease the next strongest (1-month HR 1.75 and 1-year HR of 1.78). Data from the Finnish studies<sup>98</sup> showed that pre-stroke cardiovascular disease *per se* (with the exception of atrial fibrillation) did not prove to be a predictor of death. Only those with a poor premorbid functional status (Rankin score over 2) seemed to have an increased odds ratio (OR) of 2.72 at 30 days. This encompassed all patients with disabilities causing the Rankin score to be over 2, but included cardiac and pulmonary diseases. In Quebec<sup>88</sup>, a Charlson Index<sup>110</sup> of 1 gave an OR of 1.25 for death at 8-30 days and a score of over 1 an OR of 1.66. Goldstein *et al*<sup>85</sup> demonstrated a 29% increase in the odds of death at one year for a one-point increase in the Charlson Index. The Dijon study<sup>111</sup>, however, found that previous MI (OR 1.28), hypertension (OR 1.48) or age (over 85 – OR 5.98) were all predictors of 28-day case fatality whereas AF was not. One study giving a good view of the prognostic value of premorbid conditions was performed in Rochester by Vernino *et al*<sup>108</sup>. The highest relative risks (RR) were seen in prior congestive heart failure (3.29), AF (2.47), dementia (2.32), prior MI (1.84) and angina (1.53). Immediately following cerebral infarction, chest infection gave the highest RR for death (8.08). The Copenhagen Stroke Study<sup>112</sup> found that old age (over 85) was a strong

predictor of early mortality with an OR of 2.5 and death within 5 years of stroke (OR 3.9). The authors found a higher proportion of premorbid disability and AF plus more severe strokes in those over 85, which may partly account for the results. Very little study data exists regarding the effects of specific comorbidities on stroke outcome, but it seems in general that a poor premorbid functional level is certainly a poor prognostic factor.

### **3. AIMS AND OBJECTIVES**

The intention of this thesis is to explore the effects that a comorbid diagnosis of COPD and other chronic respiratory conditions have on the survival of patients hospitalised with first stroke in Scotland.

#### **Objectives**

- To describe the baseline characteristics of individuals hospitalised with incident stroke in Scotland between 1986 and 2005
- To describe the baseline characteristics of individuals hospitalised with incident stroke in Scotland between 1986 and 2005 where there is a coexisting diagnosis of COPD/Bronchiectasis/asthma
- Compare the characteristics and survival outcomes of the two groups
- Compare distribution of causes of death between these two groups
- Describe age-standardised population-based mortality rates in stroke in Scotland

## 4. METHODS

### Data Source

The data source used for the study was taken from the Scottish Morbidity Record (SMR). The SMR is a very important episode-based record of data managed by the Information and Statistics Division (ISD), sponsored by the Scottish Executive and Department of Health. It is divided into different sections based on data source and numbered sequentially SMR01, SMR02 and so on. SMR01 comprises data from acute admissions and day-cases to Scottish hospitals. It does not include psychiatric (SMR04) or obstetric (SMR02) data. Data is recorded when a patient is discharged, changes consultant or moves to another hospital or department. The record contains both clinical and non-clinical data such as demographic details, procedure and diagnostic codes. These codes are taken from the World Health Organisation (WHO) International Classification of Diseases revisions 9 and 10 (ICD-9 & ICD-10). ICD-10 represented a significant expansion on the codes available in ICD-9 and was used in SMR data from 1996 onwards. From January 1980, SMR01 data has been linked with General Register Office for Scotland (GROS) death registrations. This is achieved by use of a computer probability matching algorithm which calculates and compares a score derived from patient identifiers (name, sex, age, date of birth, date of death, postcode and so on)<sup>113</sup>. The accuracy of SMR data is regularly reviewed by ISD. Main diagnosis coding was found to be accurate in 88% of cases of a 1.75% sample of 3 months' data checked in 2007<sup>114</sup>. Although in a database of this size inaccuracies will inevitably occur, SMR is regarded as a very useful source of data for large retrospective studies. With particular regard to stroke, Davenport *et al* found it to be satisfactory for this type of study<sup>115</sup>.

### Extraction of study data

All patients with a main diagnosis of stroke leading to admission to a Scottish hospital between 1986 and 2005 were identified. Using the linkage system, deaths linked to any of these admissions were identified up until 31<sup>st</sup> December 2005 (after which cases were right-censored). For the purposes of this study, only a patient's hospital episode with first ever stroke was counted. All other stroke hospitalisations were excluded. Comorbid conditions are determined from up to five ICD-9 or 10 codes associated with each SMR entry. These diagnoses are extracted from case notes at the time of SMR data collection.

These records, including clinical coding, dates of admission and demographic data were extracted into a separate database by the University of Glasgow Public Health unit. In the separate database of stroke hospitalisations made available to me, individual records were anonymised using unique identifiers for each case and postcode data converted to Carstairs deprivation categories.

## **Statistical analysis**

Further cleaning of the data and analysis was performed using Statistics Package for Social Sciences (SPSS Inc., Chicago, Illinois) version 15. Comorbid conditions and ICD codes for cause of death were transformed into categorical variables. Only the primary cause of death was used in the analysis. For example, death by pneumonia secondary to stroke would be listed as pneumonia alone. Each case was allocated only one cause of death. The date of death or censoring was used to calculate time to event from the admission date. The variable “respiratory comorbidity” was computed from ICD-9 and 10 codes for COPD, bronchiectasis and asthma. This group was then extracted from the main data for both separate analysis of summary statistics, demographics, comorbidity and cause of death and for comparison with the remainder of the dataset (those without these conditions). This group may be referred to as those with “respiratory comorbidity” rather than “COPD, asthma and bronchiectasis” in the remainder of this text. Kaplan-Meier plots were generated to determine if there was a significant difference in survival between patients with or without comorbid chronic respiratory conditions. The log rank test was used to confirm the statistical significance of any difference. Crude annual incidence rates were calculated using the GROS<sup>116</sup> mid-year population estimates. Standardisation to European and World population figures was undertaken using tables supplied by the University of Glasgow Public Health unit. Tables and charts were created using Microsoft Office Excel 2007 (Microsoft Corporation), with the exception of the Kaplan-Meier curves generated by SPSS.

## **Ethical Considerations**

Any identifiable information from records in the SMR was removed during creation of the database for the study. After the records have been linked with the GROS death certificate data, each one becomes a sequential case number in the new database. This information cannot be directly used to identify individual patients. Therefore there are no ethical concerns arising from this study and the use of the database for these purposes.

## 5. RESULTS

### Descriptive Statistics

#### *Annual incidence*

Year	n (crude incidence rate per 100000 per year)		
	Total	Male	Female
1986	7639 (149.44)	3283 (133.33)	4356 (164.41)
1987	7825 (153.46)	3441 (140.14)	4384 (165.83)
1988	7665 (150.96)	3336 (136.48)	4329 (164.41)
1989	7708 (151.79)	3321 (135.93)	4387 (166.49)
1990	7785 (153.21)	3370 (137.90)	4415 (167.40)
1991	7841 (154.25)	3472 (142.03)	4369 (165.57)
1992	8418 (165.53)	3794 (155.16)	4624 (175.13)
1993	8624 (169.35)	3799 (155.16)	4825 (182.49)
1994	8575 (168.06)	3709 (151.18)	4866 (183.70)
1995	8311 (162.84)	3744 (152.61)	4567 (172.32)
1996	7783 (152.84)	3542 (144.75)	4241 (160.33)
1997	8061 (158.58)	3683 (150.80)	4378 (165.77)
1998	8272 (162.93)	3822 (156.70)	4450 (168.68)
1999	8122 (160.14)	3704 (152.02)	4418 (167.64)
2000	7908 (156.19)	3668 (150.83)	4240 (161.15)
2001	7975 (157.48)	3664 (150.55)	4311 (163.89)
2002	7679 (151.92)	3458 (142.20)	4221 (160.92)
2003	7261 (143.57)	3368 (138.34)	3893 (148.43)
2004	7192 (141.62)	3305 (135.10)	3887 (147.67)
2005	6995 (137.30)	3243 (132.04)	3752 (142.19)

**Table 1 - Individuals hospitalised with 1st stroke and crude annual incidence per 100000 from 1986 to 2005**

Table 1 shows the absolute numbers admitted to Scottish hospitals each year with their first stroke and crude annual incidence rates (AIR) per 100000. In total, 157,639 individuals were admitted over the study period. This comprises 70726 men and 86913 women.

Women have a higher incidence of stroke than men for each year studied. The trend is an initial rise in incidence in the late eighties followed by two peaks in incidence for both sexes – although most marked for women. The first peak for women is the 1993-94 period at over 180 per 100000 followed by a decline in rate to 1996 (160.33 per 100000). There is then a shallower increase in incidence to 1998 (168.68 per 100000) and finally a more sustained fall in the rate to 2005. The male pattern follows a similar trend although the period 1992-2002 is more a plateau with a less distinct drop in 1996. Incidence rates for

males are similar to twenty years ago whilst there has been a marked reduction in incidence for females. Figure 1 illustrates this graphically.

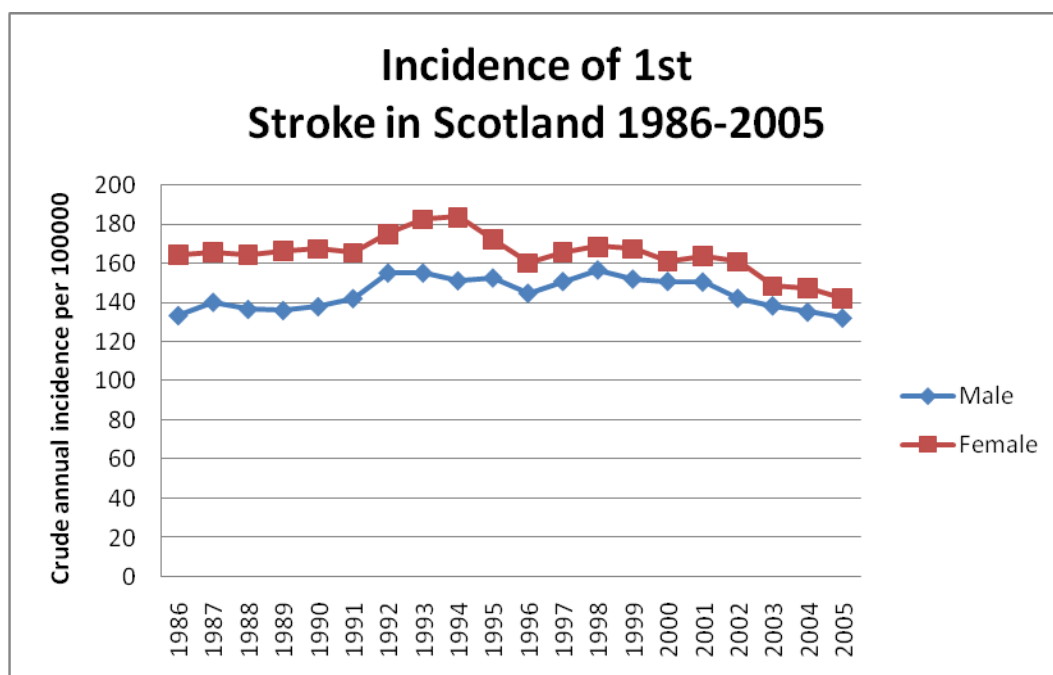


Figure 1 - Incidence rates of 1st stroke in men and women

Year	European standardised			World standardised		
	Males	Females	Total	Males	Females	Total
1986	137.2	109.1	120.4	88.4	69.8	77.5
1987	141.6	109.4	116.0	91.5	70.2	74.8
1988	136.1	106.3	113.7	88.5	68.2	73.5
1989	133.4	106.3	112.8	85.7	67.7	72.2
1990	134.7	106.7	113.2	87.7	68.3	73.1
1991	136.8	105.4	113.1	88.5	67.6	72.9
1992	149.0	111.4	121.2	96.6	71.5	78.3
1993	148.0	115.2	123.7	95.8	73.6	79.6
1994	143.6	117.1	124.1	93.6	75.9	80.7
1995	143.5	109.5	119.3	94.3	71.0	78.0
1996	134.3	101.1	111.4	87.9	65.1	72.4
1997	138.5	104.9	114.2	91.0	68.0	74.6
1998	142.1	105.7	116.9	93.6	68.7	76.6
1999	136.6	105.1	114.1	89.9	68.3	74.6
2000	133.6	100.2	110.5	88.4	64.9	72.5
2001	131.2	99.8	110.6	86.9	64.5	72.5
2002	122.2	98.4	106.0	80.5	64.2	69.5
2003	117.6	90.7	99.4	77.5	59.1	65.2
2004	113.4	88.4	96.8	75.0	57.1	63.3
2005	108.9	86.1	93.4	72.2	56.1	61.4

Table 2 - AIRs standardised to European and World population

Table 2 shows these figures standardised to the age distribution of the European and World populations. This continues to exhibit a trend comprising a peak in incidence in the early



1990s with a gradual decline in incidence towards the end of the study period. The trend from the crude figures for females to have a higher incidence rate is reversed upon standardisation. For both European and World standardised data, males have a much higher AIR than females.

## Age and sex

Ages	n (%)		
	Male	Female	Total
< 55	8992 (12.7)	7645 (8.8)	16637 (10.6)
55 - 64	12743 (18.0)	9006 (10.4)	21749 (13.8)
65 - 74	21638 (30.6)	20107 (23.1)	41745 (26.5)
75 - 84	20985 (29.7)	31880 (36.7)	52865 (33.5)
85 +	6368 (9.0)	18275 (21.0)	24643 (15.6)
Deprivation quintile			
1	11575 (16.9)	14713 (17.4)	26288 (17.2)
2	13615 (19.9)	16895 (20.0)	30510 (20.0)
3	13073 (19.1)	16118 (19.1)	29191 (19.1)
4	14351 (21.0)	17607 (20.9)	31958 (20.9)
5	15800 (23.1)	19022 (22.5)	34822 (22.8)

**Table 3 - distribution of study population by age range and deprivation quintiles**

	Age		
	Male	Female	Total
Mean (SD)	69 (13)	74 (13)	72 (13)
25th Percentile	62	68	65
75th Percentile	79	83	82
Interpercentile range	17	15	17
Range	0-113	0-111	0-111

**Table 4 - summary of age statistics for the population**

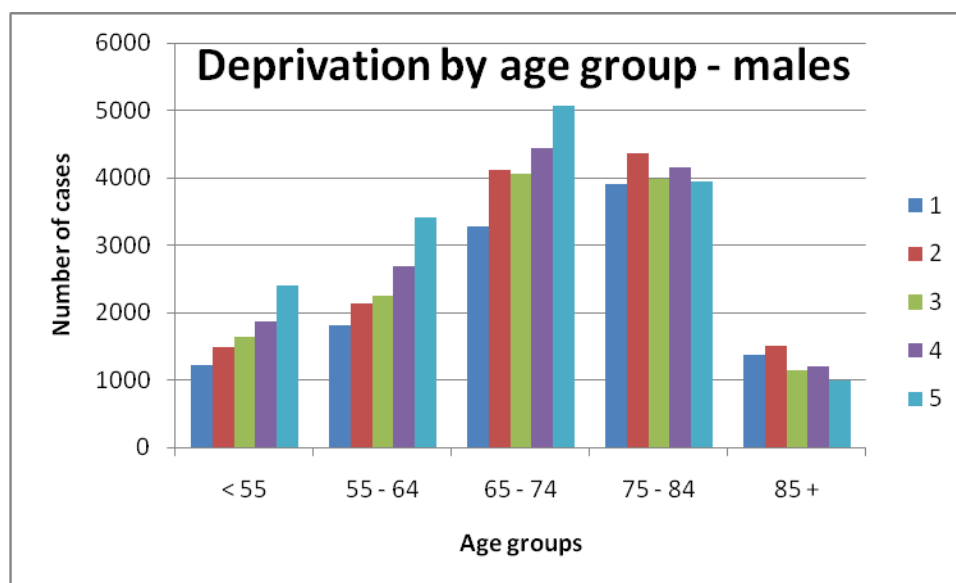
Table 3 shows how the study population is distributed amongst the defined age groups and Carstairs deprivation quintiles. It should be noted that deprivation quintiles could not be ascertained for 4870 (or 3.09%) of the records. Age statistics are presented in Table 4. The mean age for both men and women was 72 with a wide range from 0 to 111. Females were found to have a higher mean age (74 compared with 69 for men). The 25<sup>th</sup> and 75<sup>th</sup> percentiles illustrate that a quarter of patients were less than 65 years old and half the population was at an age in the range 65 to 82 years. When analysed separately, this was found to be slightly higher for women (68 to 83) than for men (62 to 79).

## Age group and deprivation categories

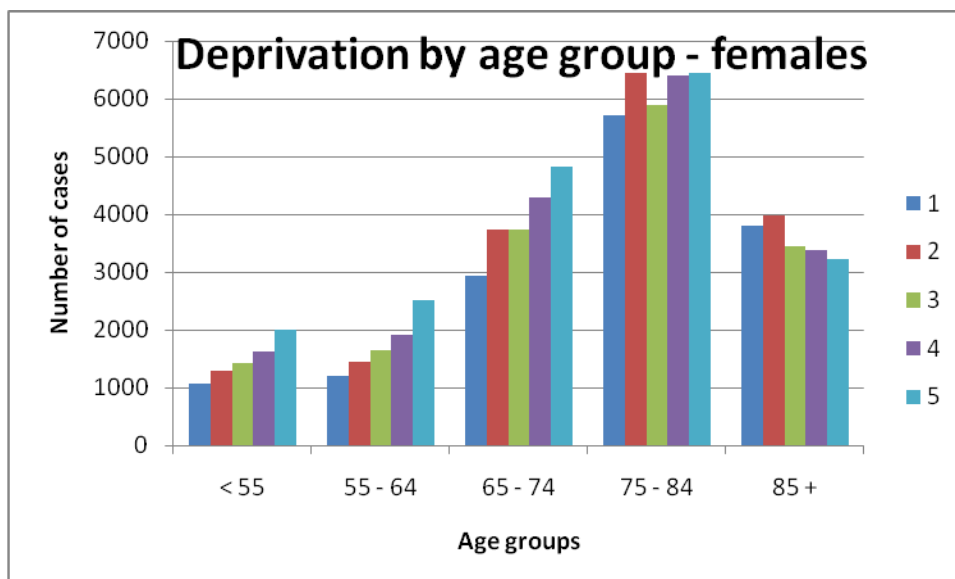
	Ages	Carstairs 1991 deprivation quintile n (%)				
		1	2	3	4	5
Male	< 55	1218 (10.5)	1495 (11.0)	1643 (12.6)	1865 (13.0)	2395 (15.2)
	55 - 64	1818 (15.7)	2139 (15.7)	2253 (17.2)	2693 (18.8)	3406 (21.6)
	65 - 74	3274 (28.3)	4116 (30.2)	4065 (31.1)	4444 (31.0)	5065 (32.1)
	75 - 84	3901 (33.7)	4362 (32.0)	3972 (30.4)	4149 (28.9)	3942 (24.9)
	85 +	1364 (11.8)	1503 (11.0)	1140 (8.7)	1200 (8.4)	992 (6.3)
Female	< 55	1077 (7.3)	1300 (7.7)	1417 (8.8)	1628 (9.2)	2007 (10.6)
	55 - 64	1201 (8.2)	1448 (8.6)	1642 (10.2)	1904 (10.8)	2518 (13.2)
	65 - 74	2933 (19.9)	3723 (22.0)	3723 (23.1)	4296 (24.4)	4826 (25.4)
	75 - 84	5702 (38.8)	6439 (38.1)	5895 (36.6)	6399 (36.3)	6455 (33.9)
	85 +	3800 (25.8)	3985 (23.6)	3441 (21.3)	3380 (19.2)	3216 (16.9)

**Table 5 - distribution of deprivation in stroke patients by age and sex group**

Table 5 displays the proportions of patients within each deprivation category by sex and age grouping. 44.1% of men and 43.4% of women are within the two most deprived categories (4 and 5). For both sexes in the age groups under 75 years, there are an increasing number of cases in the more deprived Carstairs quintiles. This gradient is much less evident in the age group 75-84 and appears to reverse in the over 85 year-olds. The pattern can be seen more clearly in Figure 2 and Figure 3.



**Figure 2 - distribution of deprivation by age group - male stroke patients**



**Figure 3 - distribution of deprivation by age group - female stroke patients**

### ***Comorbid conditions***

	n (%)		
	Male	Female	Total
Any	41654 (58.9)	49889 (57.4)	91543 (58.1)
Diabetes	6928 (9.8)	7320 (8.4)	14248 (9.0)
Cancer	5100 (7.2)	5139 (5.9)	10239 (6.5)
Respiratory Disease	5412 (7.7)	5390 (6.2)	10802 (6.9)
Heart Failure	5066 (7.2)	7035 (8.1)	12101 (7.7)
Peripheral Vascular Disease	5336 (7.5)	4478 (5.2)	9814 (6.2)
Atrial Fibrillation	7283 (10.3)	10484 (12.1)	17767 (11.3)
Hypertension	13587 (19.2)	16472 (19.0)	30059 (19.1)
Renal Failure	1927 (2.7)	2135 (2.5)	4062 (2.6)
Ischaemic Heart Disease	13733 (19.4)	13952 (16.1)	27685 (17.6)
Falls & Fracture	4224 (6.0)	9623 (11.1)	13847 (8.8)
Rheumatic/Valvular Heart Disease	1382 (2.0)	2422 (2.8)	3804 (2.4)
PE <sup>†</sup> & DVT <sup>†</sup>	1431 (2.0)	1930 (2.2)	3361 (2.1)
Depression	963 (1.4)	1838 (2.1)	2801 (1.8)
Dementia	1924 (2.7)	4234 (4.9)	6158 (3.9)
Alcohol Misuse	4172 (5.9)	1277 (1.5)	5449 (3.5)

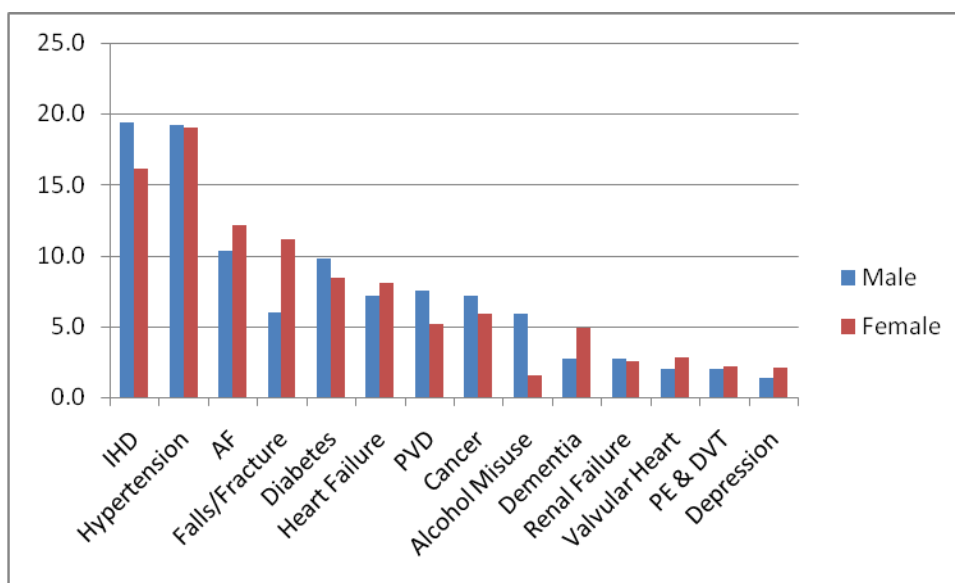
**Table 6 - distribution of comorbidities in stroke patients by sex**

Secondary diagnoses for the stroke patients are illustrated in Table 6. 58.1% of all patients had one or more comorbidity in addition to stroke. When stratified by sex, men are found

\* Pulmonary embolism

† Deep venous thrombosis

to have at least one additional diagnosis in 58.9% of cases and women in 57.4%. These data are represented graphically in Figure 4 - distribution of comorbidities in stroke patients by sex



**Figure 4 - distribution of comorbidities in stroke patients by sex**

The most common conditions present were cardiovascular; prior ischaemic heart disease (IHD), hypertension or atrial fibrillation (AF). Diabetes, respiratory disease, cancers and heart failure were next most common. Respiratory disease was recorded as being present in 6.9% of the study population (7.7% of men and 6.2% of women). Most comorbidity seems to occur with similar frequency in men and women apart from AF (more common in women), alcohol misuse (more common in men) and dementia (more common in women).

### **Stroke subtype**

	Male	Female	Total
SAH	3678 (5.2)	6435 (7.4)	10113 (6.4)
ICH	6203 (8.8)	6197 (7.1)	12400 (7.9)
CI	21392 (30.2)	22106 (25.4)	43498 (27.6)
Other	39453 (55.8)	52175 (60.0)	91628 (58.1)

**Table 7 - proportions of stroke subtypes by sex**

Table 7 shows the frequencies of the various subtypes of stroke. The most common stroke classification is “other” or undefined in 58.1% (55.8% of men and 60.0% of women). This is followed by cerebral infarction (CI; 27.6%), intracranial haemorrhage (ICH; 7.9%) and then subarachnoid haemorrhage (SAH; 6.4%). CI and “other” strokes make up 85.7% of

all strokes in the study population. The different categories of stroke seem to occur in similar proportions for both men and women.

The proportions of stroke distribution throughout the various age groupings in males and females are illustrated in Table 8. The haemorrhagic types of stroke (SAH and ICH) are far more common within the younger age groups. Infarction is fairly evenly spread and the undefined or “other” strokes are more common in the very elderly.

	Age group	Stroke type n (%)							
		SAH		ICH		CI		Other	
Male	< 55	2130	(23.7)	1373	(15.3)	2831	(31.5)	2658	(29.6)
	55 - 64	785	(6.2)	1369	(10.7)	4423	(34.7)	6166	(48.4)
	65 - 74	527	(2.4)	1727	(8.0)	6863	(31.7)	12521	(57.9)
	75 - 84	200	(1.0)	1385	(6.6)	5703	(27.2)	13697	(65.3)
	85 +	36	(0.6)	349	(5.5)	1572	(24.7)	4411	(69.3)
Female	< 55	2962	(38.7)	910	(11.9)	1859	(24.3)	1914	(25.0)
	55 - 64	1440	(16.0)	918	(10.2)	2613	(29.0)	4035	(44.8)
	65 - 74	1232	(6.1)	1625	(8.1)	5725	(28.5)	11525	(57.3)
	75 - 84	648	(2.0)	1930	(6.1)	7870	(24.7)	21432	(67.2)
	85 +	153	(0.8)	814	(4.5)	4039	(22.1)	13269	(72.6)

**Table 8 - distribution of stroke type by age category**

## ***Mortality rates***

Year	All ages		
	Males	Females	Total
1995	104.71	136.25	121.09
1996	109.68	127.02	118.69
1997	109.81	131.20	120.92
1998	110.58	130.09	120.72
1999	116.60	137.85	127.64
2000	108.35	125.50	117.26
2001	108.39	126.63	117.87
2002	106.79	131.68	119.71
2003	111.15	129.29	120.56
2004	106.04	125.87	116.32
2005	102.85	121.12	112.31

**Table 9 - Crude annual mortality rates per 100000**

Table 9 shows the crude annual mortality rates from 1995 to 2005 for both sexes. Data is only presented for the latter decade of the study. As the database only includes patients

with first stroke, not all deaths from stroke are recorded (meaning those who had a stroke before the start of the study period). Therefore the first decade would show a false rise in mortality that is not likely to be a true representation of reality. There is a rise in mortality from stroke for men and women until 1999. After this, there is a trend towards gradual reduction in the mortality rate.

Year	European standardised			World standardised		
	Males	Females	Total	Males	Females	Total
1995	96.4	79.0	86.7	60.2	48.2	53.5
1996	100.5	72.4	84.3	62.5	44.0	52.0
1997	99.1	74.8	85.3	62.0	45.5	52.8
1998	98.6	74.3	85.2	62.1	45.6	53.1
1999	102.6	78.0	89.0	64.4	47.5	55.1
2000	93.9	71.6	81.5	59.3	44.0	50.9
2001	92.7	71.5	81.0	58.8	43.9	50.7
2002	90.4	73.4	81.6	57.8	45.0	51.2
2003	93.1	72.5	81.7	58.9	44.6	51.1
2004	87.8	69.8	78.3	55.6	42.8	48.8
2005	83.0	67.7	74.9	52.6	41.8	46.8

**Table 10 - Standardised annual mortality rates per 100000**

Table 10 shows the data standardised to European and World populations. This continues to show a rise in mortality, with a plateau until a gradual reduction after 2000. Rates are consistently higher in men than in women throughout the whole of the study period.

## Stroke patients with COPD and other chronic lower respiratory tract diseases

### *Sex and age groups*

	Age		
	Male	Female	Total
Mean (SD)	73 (10)	73 (12)	73 (11)
Median	74	75	74
25th Percentile	67	67	67
75th Percentile	80	81	80
Interpercentile Range	13	14	13

**Table 11 - summary of age statistics for patients with stroke and comorbid respiratory disease**

In total, 10802 stroke patients had prior COPD, asthma or bronchiectasis recorded as being present. This comprises 5412 men and 5390 women. Age statistics for the subgroup of stroke patients with comorbid respiratory disease are summarised in Table 11. The mean age overall and for both sexes was 73. The ages of fifty percent of all patients were within the range 67 to 80 (67-80 for men and 67-81 for women).

### *Age group and deprivation categories*

Age	n (%)					
	Male		Female		Total	
< 55	272	(5.0)	368	(6.8)	640	(5.9)
55 - 64	749	(13.8)	681	(12.6)	1430	(13.2)
65 - 74	1868	(34.5)	1570	(29.1)	3438	(31.8)
75 - 84	2001	(37.0)	1978	(36.7)	3979	(36.8)
85 +	522	(9.6)	793	(14.7)	1315	(12.2)
Total	5412	(100.0)	5390	(100.0)	10802	(100.0)
Deprivation quintile						
1	706	(13.3)	661	(12.4)	1367	(12.8)
2	906	(17.0)	935	(17.6)	1841	(17.3)
3	1048	(19.7)	995	(18.7)	2043	(19.2)
4	1221	(22.9)	1231	(23.1)	2452	(23.0)
5	1446	(27.1)	1497	(28.1)	2943	(27.6)
Total	5327	(100.0)	5319	(100.0)	10646	(100.0)

**Table 12 - distribution of stroke patients with comorbid respiratory disease by sex, age and deprivation category**

The distribution for patients with respiratory comorbidity within the predefined age groups and Carstairs deprivation quintiles can be seen in Table 12. Most of the patients are between the ages of 65 and 84. Again, there is a gradient of an increasing proportion of the patients in the more deprived quintiles (4 and 5). Over half of men and women are in quintiles 4 and 5. This tendency is more marked than in the stroke patients overall. It is more evident in the age groups below 85 years.

	Age	Deprivation quintile n (%)									
		1 (least deprived)		2		3		4		5	
Male	< 55	22	(3.1)	27	(3.0)	52	(5.0)	72	(5.9)	93	(6.4)
	55 - 64	89	(12.6)	107	(11.8)	96	(9.2)	184	(15.1)	256	(17.7)
	65 - 74	216	(30.6)	319	(35.2)	369	(35.2)	404	(33.1)	539	(37.3)
	75 - 84	301	(42.6)	355	(39.2)	424	(40.5)	438	(35.9)	455	(31.5)
	85 +	78	(11.0)	98	(10.8)	107	(10.2)	123	(10.1)	103	(7.1)
Female	< 55	29	(4.4)	44	(4.7)	64	(6.4)	85	(6.9)	140	(9.4)
	55 - 64	72	(10.9)	94	(10.1)	105	(10.6)	149	(12.1)	253	(16.9)
	65 - 74	152	(23.0)	257	(27.5)	296	(29.7)	383	(31.1)	465	(31.1)
	75 - 84	267	(40.4)	379	(40.5)	371	(37.3)	458	(37.2)	473	(31.6)
	85 +	141	(21.3)	161	(17.2)	159	(16.0)	156	(12.7)	166	(11.1)

**Table 13 - distribution of age groups by deprivation category - patients with stroke and comorbid respiratory disease**

Table 13 breaks these data down by age groups and sex. There is a strong tendency for the age groups under 65 to be in the more deprived quintiles. The reverse is also true, in that older age categories are more frequently within the least deprived quintiles. The difference in proportions in least and most deprived areas is more marked for females.



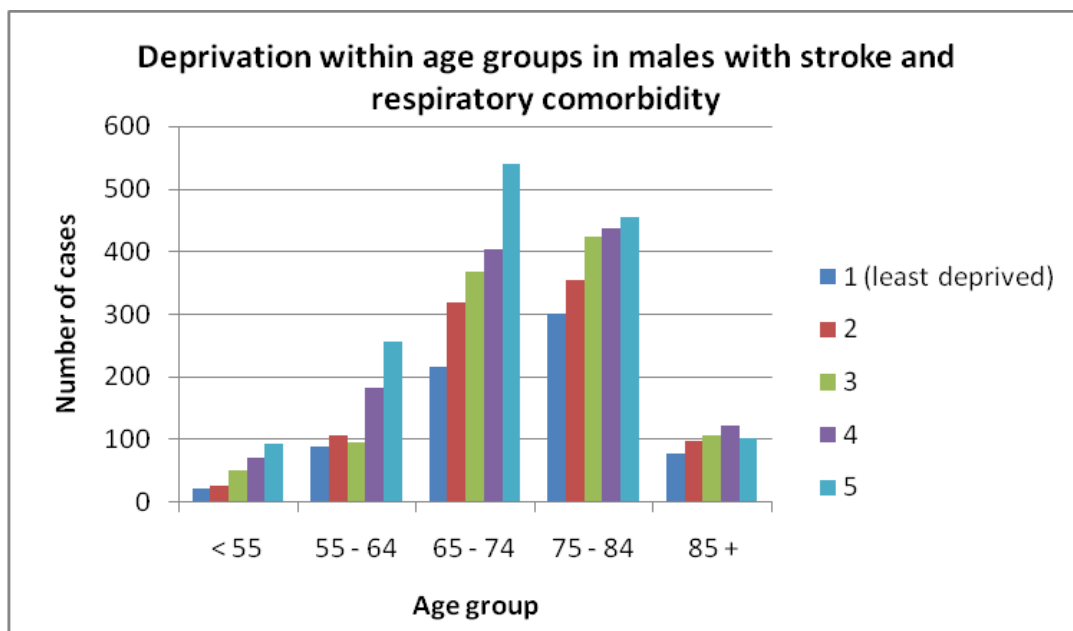


Figure 5 - deprivation within age groups - males with stroke and respiratory comorbidity

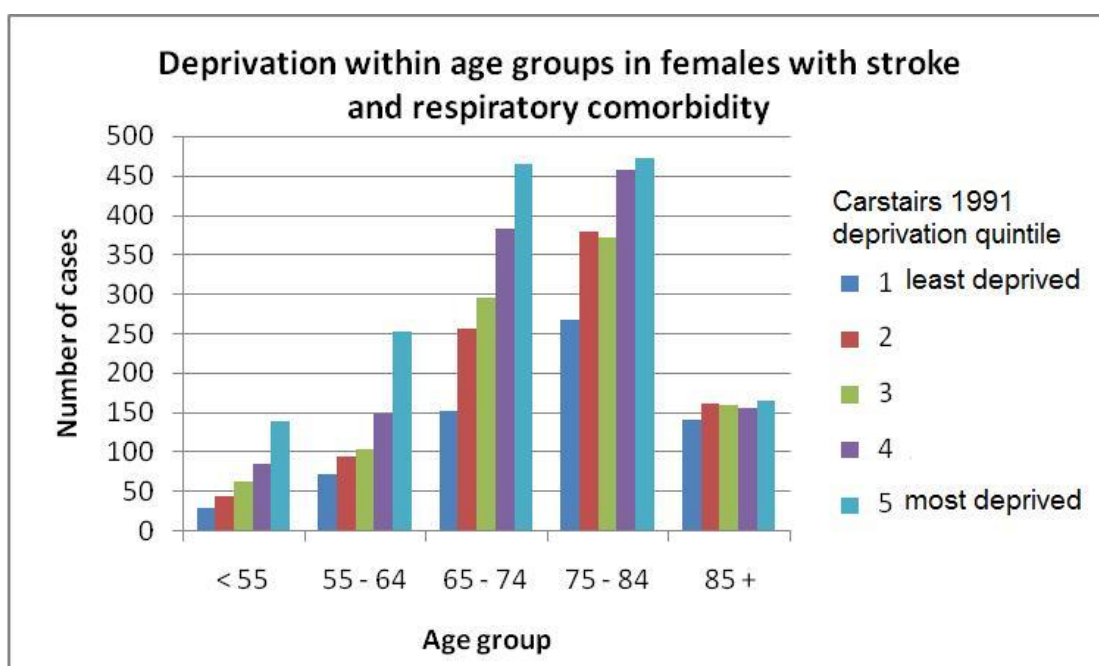
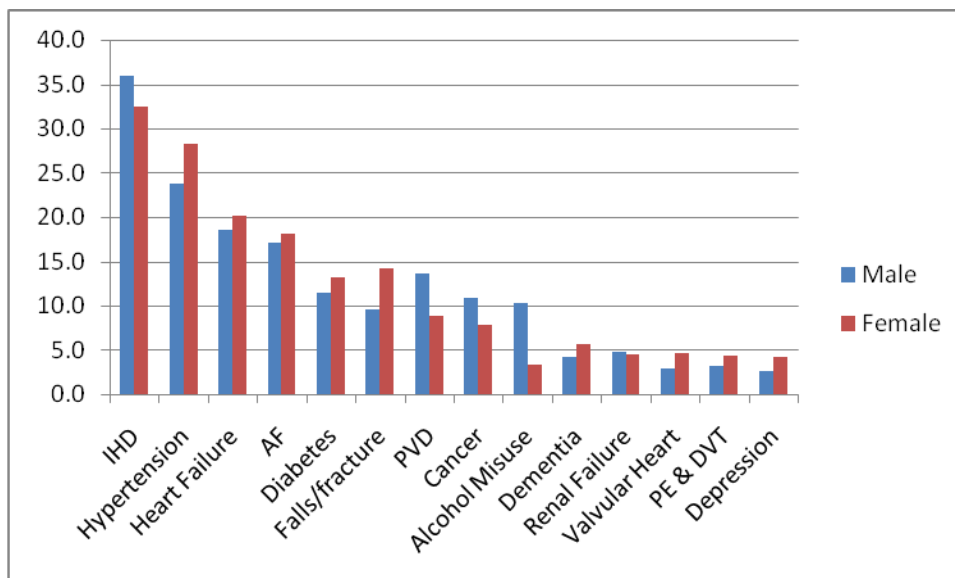


Figure 6 - deprivation within age group - females with stroke and respiratory comorbidity

### **Comorbid conditions**

8302 of the 10802 patients with prior respiratory disease had at least one other comorbidity. This includes 4152 men and 4150 women. The proportions of comorbidities present in the cohort of stroke patients with respiratory disease can be seen in Table 14 and graphically in Figure 7. As in the entire study population, IHD and hypertension are the two most commonly occurring conditions. Overall, there is a much higher level of other comorbidities present in this subgroup with prior respiratory disease. Notably, heart failure

is over twice as common in the respiratory disease cohort and AF, IHD and peripheral vascular disease (PVD) are almost twice as common.



**Figure 7 - other conditions in stroke patients with prior respiratory comorbidity**

	Male	Female	Total
Diabetes	623 (11.5)	711 (13.2)	1334 (12.3)
Cancer	591 (10.9)	421 (7.8)	1012 (9.4)
Heart Failure	1003 (18.5)	1081 (20.1)	2084 (19.3)
Peripheral Vascular Disease	723 (13.6)	481 (8.9)	1204 (11.1)
Atrial Fibrillation	928 (17.1)	979 (18.1)	1907 (17.7)
Essential Hypertension	1281 (23.7)	1520 (28.2)	2801 (25.9)
Renal Failure	259 (4.8)	245 (4.5)	504 (4.7)
Ischaemic Heart Disease	1945 (35.9)	1744 (32.4)	3689 (34.2)
Rheumatic/Valvular Heart Disease	155 (2.9)	256 (4.7)	411 (3.8)
Pulmonary Embolism & DVT	171 (3.2)	234 (4.3)	405 (3.7)
Depression	140 (2.6)	224 (4.2)	364 (3.4)
Dementia	229 (4.2)	301 (5.6)	530 (4.9)
Falls & Fracture	519 (9.6)	765 (14.2)	1284 (11.9)
Alcohol Misuse	560 (10.3)	172 (3.3)	732 (6.8)

**Table 14 - distribution of other conditions amongst stroke patients with respiratory comorbidity**

## Stroke subtype

The distribution of stroke subtypes by sex can be seen in Table 15. The proportion of SAH in these patients compared to all stroke patients is smaller. The remaining stroke categories are in similar proportions between the whole study population and this cohort. The undefined or “other” strokes are the most common; 57.1% in men, 56.0% in women and 56.5% over all. Cerebral infarction is the next most common; 33.5% of men, 32.9% of women and 32.9% altogether. CI and “other” strokes account for 89.7% of all strokes in individuals with prior respiratory disease.

	Male	Female	Total
SAH	111 (2.1)	247 (4.6)	358 (3.3)
ICH	400 (7.4)	351 (6.5)	751 (7.0)
CI	1812 (33.5)	1774 (32.9)	3586 (33.2)
Other	3089 (57.1)	3018 (56.0)	6107 (56.5)

**Table 15 - distribution of stroke subtype in patients with respiratory comorbidity**

In Table 16, the distribution of stroke subtype amongst the age categories can be seen. As in the whole stroke study population, the haemorrhagic stroke types are more common in the younger age groups. However, this is to a lesser extent in the respiratory comorbidity subgroup in comparison to the entire study population. Cerebral infarction is more common across all age groups than was seen in the parent population. The undefined or “other” category of stroke is slightly more common also, but only in the two youngest age groups.

	Age group	Stroke type n (%)			
		SAH	ICH	CI	Other
Male	< 55	33 (12.1)	34 (12.5)	109 (40.1)	96 (35.3)
	55 - 64	39 (5.2)	72 (9.6)	260 (34.7)	378 (50.5)
	65 - 74	23 (1.2)	141 (7.5)	668 (35.8)	1036 (55.5)
	75 - 84	12 (0.6)	118 (5.9)	631 (31.5)	1240 (62.0)
	85 +	4 (0.8)	35 (6.7)	144 (27.6)	339 (64.9)
Female	< 55	82 (20.6)	39 (9.8)	133 (33.4)	144 (36.2)
	55 - 64	61 (9.0)	52 (7.6)	240 (35.2)	328 (48.2)
	65 - 74	69 (4.4)	111 (7.1)	581 (37.0)	809 (51.5)
	75 - 84	29 (1.5)	117 (5.9)	604 (30.5)	1228 (62.1)
	85 +	6 (0.8)	32 (4.0)	216 (27.2)	539 (68.0)

**Table 16 - distribution of stroke subtype by age groups in patients with respiratory comorbidity**

# Survival

## ***Stroke patients***

Out of the 157639 stroke patients, only 41860 (26.6%) were still alive at the end of the study period. The overall survival rate to 30 days was 74.1% (95% CI<sup>‡</sup> 74.0-74.2), to 1 year was 58.1% (95% CI 58.0-58.2) and to 5 years was 35.2% (95% CI 35.1-35.3). A breakdown of survival data by age group and deprivation quintile is provided in Table 17.

		Survival (% (95% CI))		
		30 days	1 year	5 years
Age category	All	74.1 (74.0 to 74.2)	58.1 (58.0 to 58.2)	35.2 (35.1 to 35.3)
	< 55	83.5 (83.2 to 83.8)	80.2 (79.9 to 80.5)	72.2 (71.8 to 72.5)
	55 - 64	81.6 (81.3 to 81.9)	73.8 (73.5 to 74.1)	57.1 (56.7 to 57.4)
	65 - 74	76.8 (76.6 to 77.0)	63.5 (63.2 to 63.7)	39.9 (39.6 to 40.1)
	75 - 84	70.7 (70.5 to 70.9)	50.6 (50.4 to 50.9)	23.6 (23.4 to 23.8)
	85 +	64.0 (63.7 to 64.3)	36.6 (36.3 to 36.9)	11.2 (11.0 to 11.4)
Deprivation quintile	1	74.5 (74.3 to 74.8)	58.1 (57.8 to 58.4)	34.9 (34.6 to 35.2)
	2	73.5 (73.2 to 73.7)	57.0 (56.7 to 57.3)	33.9 (33.7 to 34.2)
	3	73.6 (73.3 to 73.8)	57.7 (57.4 to 58.0)	34.6 (34.3 to 34.9)
	4	73.9 (73.6 to 74.1)	57.8 (57.5 to 58.0)	35.1 (34.8 to 35.3)
	5	75.4 (75.2 to 75.6)	59.4 (59.2 to 59.7)	35.8 (35.6 to 36.1)

**Table 17 - unadjusted survival of stroke patients by age and deprivation**

There exists a decreasing gradient of survival with increasing age both in the short and long term. This is especially evident at 5 years. At this point, only 11.2% (95% CI 11.0-11.4) of those aged over 85 years were still alive compared with 72.2% (95% CI 71.8-72.5) of those aged under 55 years. Survival rates at each time point are very similar for the deprivation quintiles and there is little difference in survival between the most and least deprived categories.

The 30 day, 1 and 5 year survival data is further stratified by gender in Table 18. Males have a higher survival rate than females in most age groups and deprivation categories, though this tendency is only slight and is less evident with increasing age. Again, although the pattern for higher survival in males than females is still evident, there is little variation in survival from the more deprived to the less deprived categories.

The survival data for each of the comorbidities is available in Table 19. At 30 days there is only a slight difference in survival between those with no comorbidity and those with one or more. This difference increases at 1 year and further still at 5 years where there is an

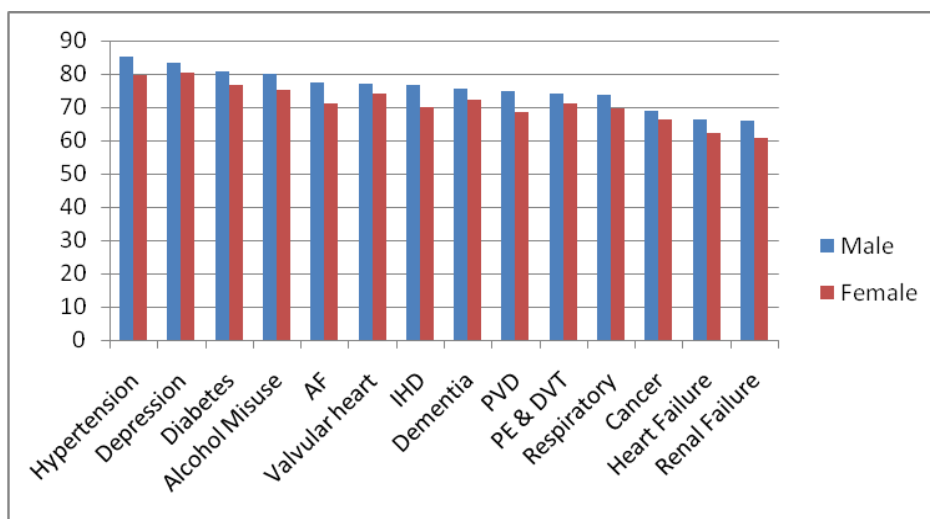
<sup>‡</sup> CI – Confidence interval

almost 10% higher survival rate for men and women. For 30 days, 1 year and 5 year follow up; survival is highest amongst those men and women with prior hypertension. This is followed (in decreasing order of survival) by depression, diabetes mellitus and alcohol misuse. Respiratory disease, heart failure, renal failure and dementia are consistently the comorbidities associated with worse survival at 30 days, 1 and 5 years.

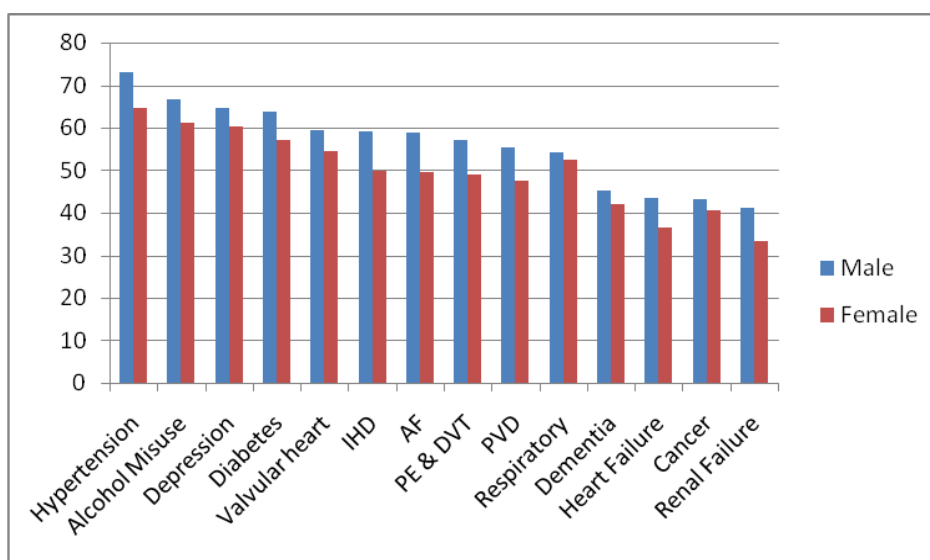
		Survival (% (95% CI))					
		30 days		1 year		5 years	
		Male	Female	Male	Female	Male	Female
Age category	All	77.0 (76.8 to 77.2)	71.8 (71.6 to 71.9)	62.1 (61.9 to 62.3)	54.9 (54.7 to 55.0)	38.6 (38.5 to 38.8)	32.5 (32.3 to 32.6)
	< 55	84.7 (84.4 to 85.1)	82.1 (81.7 to 82.5)	81.3 (80.8 to 81.7)	78.9 (78.5 to 79.4)	71.9 (71.4 to 72.4)	72.5 (72.0 to 73.1)
	55 - 64	83.5 (83.2 to 83.9)	78.9 (78.4 to 79.3)	75.8 (75.4 to 76.1)	71.1 (70.7 to 71.6)	57.7 (57.3 to 58.2)	56.1 (55.5 to 56.6)
	65 - 74	78.5 (78.2 to 78.8)	75.0 (74.7 to 75.3)	64.8 (64.5 to 65.1)	62.0 (61.7 to 62.3)	39.7 (39.3 to 40.0)	40.1 (39.8 to 40.5)
	75 - 84	71.9 (71.6 to 72.2)	69.9 (69.6 to 70.1)	50.7 (50.4 to 51.0)	50.6 (50.3 to 50.9)	22.1 (21.8 to 22.4)	24.5 (24.3 to 24.8)
	85 +	64.8 (64.2 to 65.4)	63.7 (63.4 to 64.1)	36.5 (35.9 to 37.1)	36.7 (36.3 to 37.0)	10.0 (9.6 to 10.4)	11.6 (11.4 to 11.8)
Deprivation quintile	1	77.0 (76.6 to 77.4)	72.6 (72.2 to 72.9)	62.0 (61.6 to 62.5)	55.0 (54.6 to 55.4)	38.5 (38.1 to 39.0)	32.2 (31.8 to 32.5)
	2	76.1 (75.8 to 76.5)	71.3 (71.0 to 71.7)	60.8 (60.3 to 61.2)	54.0 (53.6 to 54.4)	37.1 (36.7 to 37.5)	31.4 (31.1 to 31.8)
	3	76.7 (76.3 to 77.0)	71.0 (70.7 to 71.4)	61.7 (61.3 to 62.1)	54.5 (54.1 to 54.9)	38.2 (37.7 to 38.6)	31.8 (31.4 to 32.2)
	4	77.0 (76.6 to 77.3)	71.4 (71.1 to 71.7)	61.7 (61.3 to 62.1)	54.5 (54.2 to 54.9)	38.5 (38.0 to 38.9)	32.3 (31.9 to 32.7)
	5	78.4 (78.0 to 78.7)	72.9 (72.6 to 73.2)	63.4 (63.0 to 63.8)	56.2 (55.8 to 56.5)	38.7 (38.3 to 39.1)	33.5 (33.2 to 33.9)

**Table 18 - unadjusted survival of stroke patients by age, sex and deprivation**

The difference in survival between the comorbidity associated with the highest rate and that associated with the lowest rate becomes more marked at 1 year and even more so at 5 years. For instance, survival in men with stroke and hypertension at 1 year is 73.1% (95% CI 72.7-73.5) compared with the lowest survival rate in men with stroke and renal failure at 41.3% (95% CI 40.1-42.4). A similar comparison for men at 5 years is the highest rate of survival in hypertension; 48.3% (95% CI 47.9-48.8) versus the lowest survival in dementia; 15.1% (95% CI 14.3-16.0). This can be seen graphically in Figure 8, Figure 9 and Figure 10.



**Figure 8 - 30 day stroke survival rates for each comorbidity**

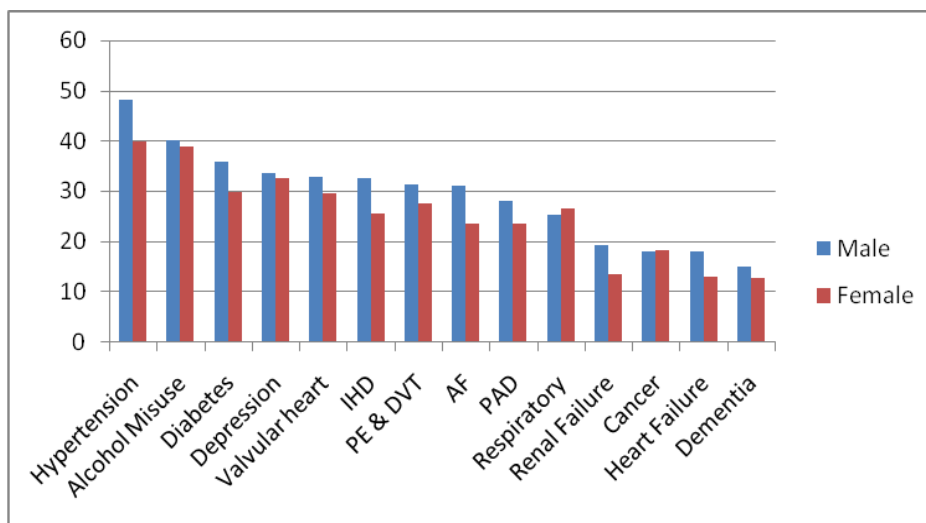


**Figure 9 - 1 year stroke survival rates for each comorbidity**

	Survival (% (95% CI))					
	30 days		1 year		5 years	
	Male	Female	Male	Female	Male	Female
None	76.0 (75.7 to 76.2)	70.7 (70.5 to 70.9)	63.5 (63.2 to 63.8)	57.3 (57.0 to 57.5)	43.5 (43.2 to 43.8)	38.0 (37.7 to 38.3)
Any	77.7 (77.5 to 77.9)	72.5 (72.3 to 72.7)	61.1 (60.9 to 61.3)	53.1 (52.9 to 53.3)	35.1 (34.9 to 35.4)	28.3 (28.1 to 28.5)
Diabetes	80.8 (80.3 to 81.3)	76.6 (76.1 to 77.1)	63.9 (63.3 to 64.5)	57.1 (56.6 to 57.7)	35.9 (35.3 to 36.5)	30.0 (29.4 to 30.5)
Cancer	69.0 (68.3 to 69.6)	66.2 (65.5 to 66.8)	43.1 (42.4 to 43.8)	40.5 (39.8 to 41.2)	18.2 (17.7 to 18.8)	18.3 (17.7 to 18.8)
Respiratory	73.7 (73.1 to 74.3)	69.8 (69.2 to 70.4)	54.3 (53.6 to 55.0)	52.6 (51.9 to 53.3)	25.4 (24.8 to 26.0)	26.5 (25.9 to 27.1)
Heart Failure	66.3 (65.6 to 67.0)	62.2 (61.6 to 62.7)	43.6 (42.9 to 44.3)	36.5 (35.9 to 37.1)	18.1 (17.6 to 18.7)	13.1 (12.7 to 13.5)
PVD	74.9 (74.3 to 75.5)	68.6 (67.9 to 69.3)	55.5 (54.8 to 56.2)	47.4 (46.7 to 48.2)	28.0 (27.4 to 28.6)	23.7 (23.0 to 24.3)
AF	77.4 (76.9 to 77.9)	71.2 (70.8 to 71.7)	58.9 (58.4 to 59.5)	49.5 (49.0 to 50.0)	31.1 (30.6 to 31.7)	23.7 (23.3 to 24.1)
Essential Hypertension	85.0 (84.7 to 85.3)	79.6 (79.3 to 79.9)	73.1 (72.7 to 73.5)	64.5 (64.2 to 64.9)	48.3 (47.9 to 48.8)	39.8 (39.4 to 40.2)
Renal Failure	65.8 (64.7 to 66.9)	60.6 (59.6 to 61.7)	41.3 (40.1 to 42.4)	33.4 (32.4 to 34.4)	19.3 (18.3 to 20.2)	13.6 (12.9 to 14.4)
Ischaemic Heart Disease	76.5 (76.2 to 76.9)	70.0 (69.7 to 70.4)	59.1 (58.7 to 59.6)	49.9 (49.5 to 50.3)	32.7 (32.3 to 33.1)	25.5 (25.1 to 25.9)
Valvular Heart Disease	76.9 (75.7 to 78.0)	74.0 (73.1 to 74.9)	59.3 (58.0 to 60.7)	54.6 (53.6 to 55.6)	32.8 (31.4 to 34.1)	29.5 (28.6 to 30.5)
PE & DVT	74.0 (72.8 to 75.2)	71.1 (70.1 to 72.2)	57.2 (55.9 to 58.6)	49.0 (47.8 to 50.1)	31.5 (30.2 to 32.8)	27.6 (26.5 to 28.6)
Depression	83.5 (82.3 to 84.7)	80.4 (79.5 to 81.3)	64.6 (63.1 to 66.2)	60.3 (59.2 to 61.5)	33.6 (32.0 to 35.2)	32.7 (31.6 to 33.9)
Dementia	75.4 (74.5 to 76.4)	72.1 (71.4 to 72.8)	45.2 (44.1 to 46.3)	42.1 (41.3 to 42.8)	15.1 (14.3 to 16.0)	12.9 (12.4 to 13.4)
Alcohol Misuse	80.1 (79.5 to 80.7)	75.3 (74.1 to 76.5)	66.7 (65.9 to 67.4)	61.2 (59.8 to 62.6)	40.1 (39.3 to 40.9)	38.8 (37.3 to 40.2)

**Table 19 - unadjusted survival by prior comorbidity and sex**





**Figure 10 - 5 year stroke survival rates for each comorbidity**

	Survival (% (95% CI))					
	30 days		1 year		5 years	
	Male	Female	Male	Female	Male	Female
SAH	72.7 (72.0 to 73.5)	69.9 (69.3 to 70.5)	68.6 (67.9 to 69.4)	64.2 (63.6 to 64.8)	60.4 (59.6 to 61.3)	56.1 (55.4 to 56.7)
ICH	59.5 (58.9 to 60.1)	53.9 (53.3 to 54.6)	49.8 (49.1 to 50.4)	42.6 (41.9 to 43.2)	33.6 (33.0 to 34.2)	27.0 (26.5 to 27.6)
CI	88.7 (88.5 to 88.9)	85.4 (85.2 to 85.7)	75.3 (75.0 to 75.6)	68.8 (68.5 to 69.1)	49.2 (48.8 to 49.6)	42.8 (42.5 to 43.2)
Other	73.8 (73.6 to 74.0)	68.3 (68.1 to 68.5)	56.4 (56.2 to 56.7)	49.4 (49.2 to 49.6)	32.3 (32.0 to 32.5)	26.3 (26.1 to 26.5)

**Table 20 - unadjusted survival by stroke subtype and sex**

Table 20 presents an analysis of survival within each of the stroke subtypes. At 30 days and 1 year, CI is associated with the most favourable survival rate and ICH with the least favourable rates. However, survival is highest in those patients with SAH at 5 years and lowest in those with “other” stroke.

### ***Stroke patients with COPD and other chronic lower respiratory tract diseases***

		Survival (% (95% CI))		
		30 days	1 year	5 years
	All	71.8 (71.3 to 72.2)	53.5 (53.0 to 54.0)	25.9 (25.5 to 26.4)
Age group	< 55	84.5 (83.1 to 85.9)	79.1 (77.5 to 80.8)	65.7 (63.7 to 67.8)
	55 - 64	80.2 (79.1 to 81.2)	70.6 (69.4 to 71.8)	47.7 (46.3 to 49.1)
	65 - 74	74.4 (73.6 to 75.1)	58.0 (57.2 to 58.9)	28.5 (27.7 to 29.3)
	75 - 84	67.6 (66.9 to 68.4)	46.3 (45.5 to 47.1)	16.6 (16.0 to 17.2)
	85 +	62.2 (60.8 to 63.5)	33.1 (31.8 to 34.4)	8.4 (7.6 to 9.1)
Deprivation quintile	1	72.6 (71.4 to 73.8)	54.3 (52.9 to 55.7)	25.5 (24.3 to 26.7)
	2	70.6 (69.6 to 71.7)	50.5 (49.4 to 51.7)	24.5 (23.4 to 25.5)
	3	70.3 (69.3 to 71.3)	52.2 (51.1 to 53.3)	25.7 (24.7 to 26.7)
	4	72.0 (71.1 to 72.9)	53.4 (52.4 to 54.4)	26.1 (25.2 to 27.1)
	5	73.0 (72.2 to 73.9)	56.0 (55.1 to 56.9)	26.7 (25.8 to 27.5)

**Table 21 - unadjusted survival by age and deprivation - stroke patients with respiratory comorbidity**

Corresponding survival data at 30 days, 1 year and 5 years for the stroke patients with respiratory comorbidity are presented in Table 21. Overall survival for both sexes was 71.8% (95% CI 71.3 to 72.2) at 30 days, 53.5 (95% CI 53.0 to 54.0) at 1 year and 25.9 (95% CI 25.5 to 26.4) at 5 years. As with the parent population, survival is lower with each older age category. The survival rates reduce strikingly at 1 year and further still at 5 years and are consistently lower than those for the whole population. The confidence intervals do not cross those of the parent population in any of the age categories apart from less than 55 years at 30 days and one year. Otherwise, survival is significantly lower for all the other ages at each time point. There is a suggestion of decreasing survival with the more deprived deprivation quintiles, but again the confidence intervals overlap widely, making this pattern non-significant.

Table 22 presents the data from Table 21 divided into male and female categories. Males have a higher survival than females at most points (in terms of age, deprivation quintile and at each time point). This is less so at 5 years where females appear to have a survival advantage in some categories (50.3 (95% CI 48.3 to 52.4) for females age 55-64 compared with 45.5 (95% CI 43.6 to 47.4) for males). Females also have higher survival at ages 75-84 and over 85 years, with non-overlapping confidence intervals. As with the data for both sexes, when survival and deprivation is analysed by sex, there is no gradient of survival across the quintiles.

In Table 23, the survival data is tabulated by sex and stroke type as before. There is no difference between male and female survival for SAH at any endpoint. For ICH, only at 30 days do men have a higher survival rate with there being no significant sex difference at 1 or 5 years. Males have a greater survival rate than females with CI at 30 days and 1 year, but not at 5 years where the confidence intervals overlap and there is no significant difference. Females have higher survival rates than males for “other” strokes at 5 years, but at 30 days and 1 year, male survival is greater. Both sexes with chronic respiratory diseases have a poorer survival for all strokes at 30 days, 1 and 5 years when compared with the whole population. Survival from ICH is poorest at 30 days and 1 year, with “other” strokes being least survivable at 5 years by both sexes. The best prognosis is from CI at 30 days and 1 year, with SAH having the highest proportion of both sexes surviving at 5 years. The pattern here for those with chronic respiratory comorbidity is similar to that of the whole population.

		Survival (% (95% CI))					
		30 days		1 year		5 years	
		Male	Female	Male	Female	Male	Female
	All	73.7 (73.1 to 74.3)	69.8 (69.2 to 70.4)	54.3 (53.6 to 55.0)	52.6 (51.9 to 53.3)	25.4 (24.8 to 26.0)	26.5 (25.9 to 27.1)
Age group	< 55	86.3 (84.3 to 88.4)	83.1 (81.2 to 85.1)	80.4 (77.9 to 82.8)	78.2 (76.0 to 80.4)	65.9 (62.8 to 69.0)	65.6 (62.9 to 68.3)
	55 - 64	79.9 (78.5 to 81.4)	80.4 (78.9 to 82.0)	70.0 (68.3 to 71.7)	71.3 (69.5 to 73.0)	45.5 (43.6 to 47.4)	50.3 (48.3 to 52.4)
	65 - 74	76.2 (75.2 to 77.2)	72.2 (71.1 to 73.3)	58.7 (57.6 to 59.9)	57.2 (55.9 to 58.4)	28.6 (27.5 to 29.7)	28.4 (27.2 to 29.6)
	75 - 84	70.0 (69.0 to 71.1)	65.2 (64.2 to 66.3)	46.6 (45.5 to 47.7)	45.9 (44.8 to 47.0)	15.1 (14.3 to 16.0)	18.1 (17.2 to 19.0)
	85 +	63.8 (61.7 to 65.9)	61.1 (59.4 to 62.8)	32.9 (30.9 to 35.0)	33.2 (31.6 to 34.9)	7.3 (6.1 to 8.4)	9.1 (8.1 to 10.1)
Deprivation quintile	1	74.2 (72.5 to 75.8)	70.9 (69.1 to 72.7)	54.7 (52.8 to 56.6)	53.9 (52.0 to 55.9)	24.9 (23.3 to 26.6)	26.1 (24.3 to 27.9)
	2	73.6 (72.1 to 75.0)	67.8 (66.3 to 69.3)	52.9 (51.2 to 54.5)	48.3 (46.6 to 49.9)	24.6 (23.1 to 26.1)	24.4 (22.9 to 25.8)
	3	71.5 (70.1 to 72.9)	69.0 (67.5 to 70.5)	52.1 (50.5 to 53.6)	52.4 (50.8 to 53.9)	24.0 (22.6 to 25.4)	27.5 (26.1 to 29.0)
	4	73.8 (72.5 to 75.0)	70.3 (69.0 to 71.6)	53.7 (52.2 to 55.1)	53.1 (51.7 to 54.6)	26.2 (24.9 to 27.5)	26.1 (24.8 to 27.4)
	5	75.8 (74.6 to 76.9)	70.4 (69.2 to 71.6)	57.6 (56.3 to 58.9)	54.5 (53.2 to 55.8)	26.0 (24.8 to 27.2)	27.3 (26.1 to 28.5)

**Table 22 - unadjusted survival by sex, age and deprivation - stroke patients with respiratory comorbidity**

	Survival (% (95% CI))					
	30 days		1 year		5 years	
	Male	Female	Male	Female	Male	Female
SAH	66.7 (62.2 to 71.1)	67.9 (64.9 to 70.9)	59.4 (54.7 to 64.2)	61.0 (57.8 to 64.2)	47.4 (42.4 to 52.5)	44.7 (41.3 to 48.1)
ICH	57.9 (55.4 to 60.4)	54.7 (52.0 to 57.4)	43.8 (41.3 to 46.3)	41.6 (38.9 to 44.3)	21.1 (19.0 to 23.2)	22.2 (19.9 to 24.5)
CI	85.6 (84.7 to 86.4)	83.3 (82.4 to 84.2)	68.0 (66.9 to 69.1)	66.4 (65.2 to 67.5)	35.6 (34.4 to 36.8)	35.1 (33.9 to 36.3)
Other	69.1 (68.3 to 70.0)	63.8 (62.9 to 64.7)	47.7 (46.8 to 48.6)	45.3 (44.3 to 46.2)	19.7 (18.9 to 20.4)	20.9 (20.2 to 21.7)

**Table 23 - unadjusted survival by sex and stroke subtype - patients with respiratory comorbidity**

## Kaplan Meier (KM) survival curves

### Survival – all patients with and without respiratory disease

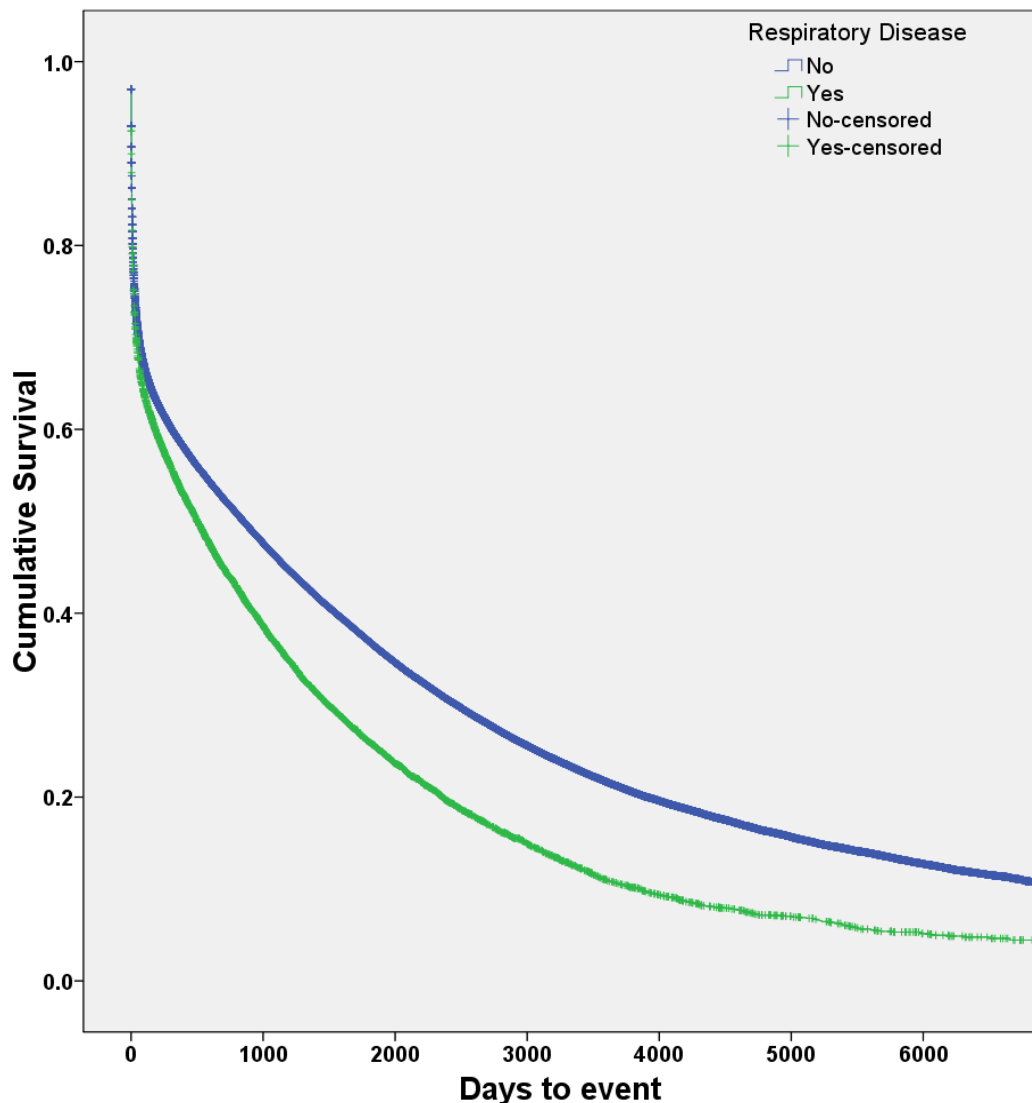


Figure 11 - Kaplan-Meier (KM) plot of survival of stroke patients with and without respiratory comorbidity

Figure 11 is a KM plot for all patients followed up to 7000 days. The two curves compare survival for those with respiratory disease to those without respiratory disease. Early on, there is a definite divergence in that patients with respiratory comorbidity clearly have a poorer survival at each time point. The median survival (see Table 24) for those with a stroke and no respiratory comorbidity was 851 days (95% CI 835 to 867) and for those with respiratory comorbidity was 501 days (95% CI 466 to 536). This was statistically significant by the log rank test (p-value <0.001). Figure 12 and Figure 13 show the KM plots for each sex. The difference in survival between respiratory comorbidity and no respiratory comorbidity is greater for males than for females, and overall survival in females is worse than males. Median survival for all males was 1051 days (95% CI 1027

to 1075) and for females was 630 days (95% CI 611 to 649). Comparing no prior respiratory disease to respiratory disease respectively; for males survival was 1119 days (95% CI 1093 to 1145) without and 517 days (95% CI 471 to 563) with respiratory comorbidity and for females 644 days (95% CI 624 to 664) without and 490 days (95% CI 436 to 544) with respiratory disease.

### **KM plots by sex**

Figure 12 plots the survival of the two groups studied for females and Figure 13 shows the same data for males.

### **KM plots by age group**

Figure 14 shows the KM plot for respiratory comorbidity against no prior respiratory comorbidity for the under 55 age group, Figure 15 for the group 55 to 64, Figure 16 for the 65 to 74 group, Figure 17 for ages 75 to 84 and Figure 18 for those aged 85 and over. A significant difference (p-value <0.001) is seen between the two groups at each range of age. This difference diminishes with increasing age group, but is still significant.

### **KM plots by age group**

Figure 14 shows the KM plot for respiratory comorbidity against no prior respiratory comorbidity for the under 55 age group, Figure 15 for the group 55 to 64, Figure 16 for the 65 to 74 group, Figure 17 for ages 75 to 84 and Figure 18 for those aged 85 and over. A significant difference (p-value <0.001) is seen between the two groups at each range of age. This difference diminishes with increasing age group, but is still significant.

### **KM plots by deprivation category**

Figure 19, Figure 20, Figure 21, Figure 22, Figure 23 compare the KM survival curves for those with or without respiratory comorbidity for Carstairs Deprivation Quintiles 1 through 5 in ascending order. The difference in survival remains (in that individuals with respiratory illnesses have poorer survival) but the curves are similar for all quintiles with no clear difference between the least and most deprived quintiles.

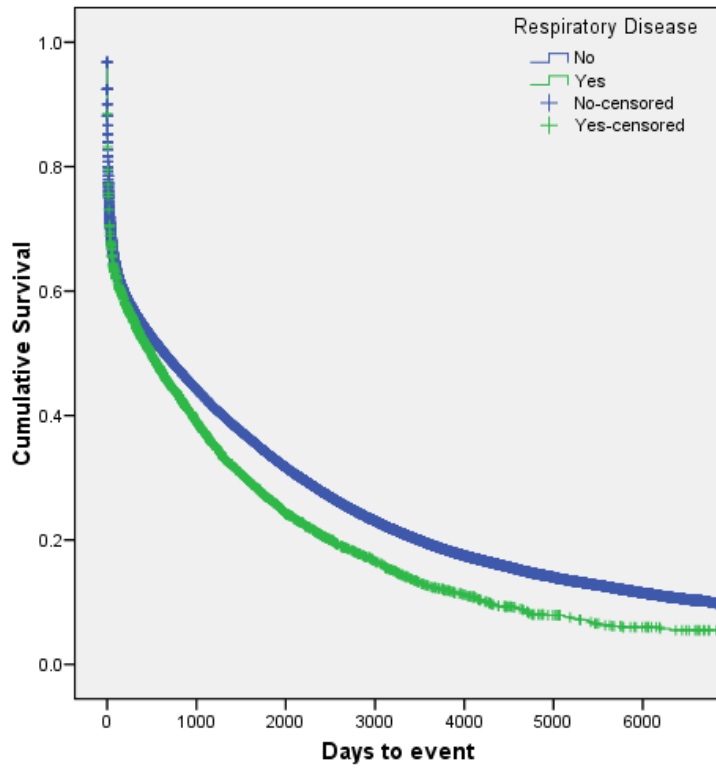


Figure 12 - KM plot for females with and without respiratory comorbidity

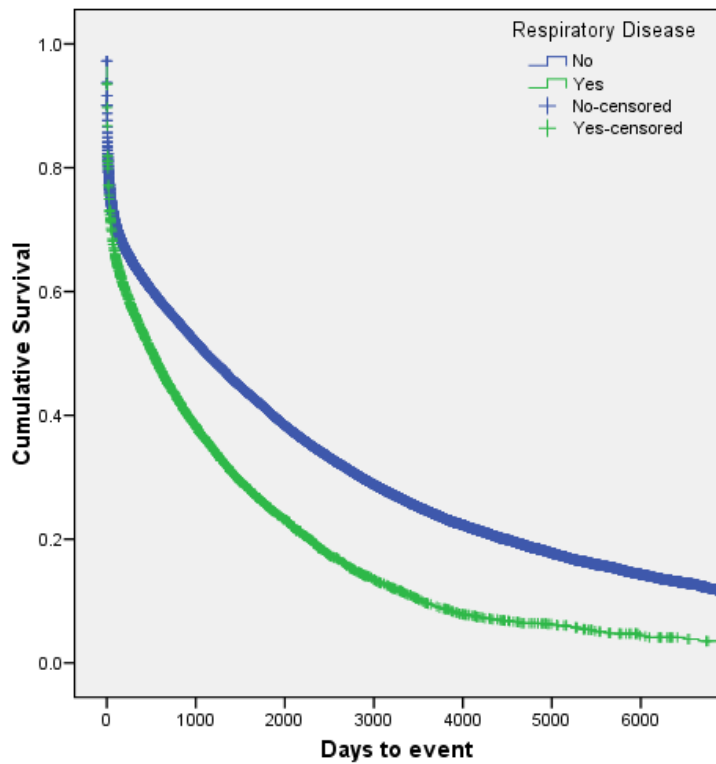


Figure 13 - KM plot for males with and without respiratory comorbidity

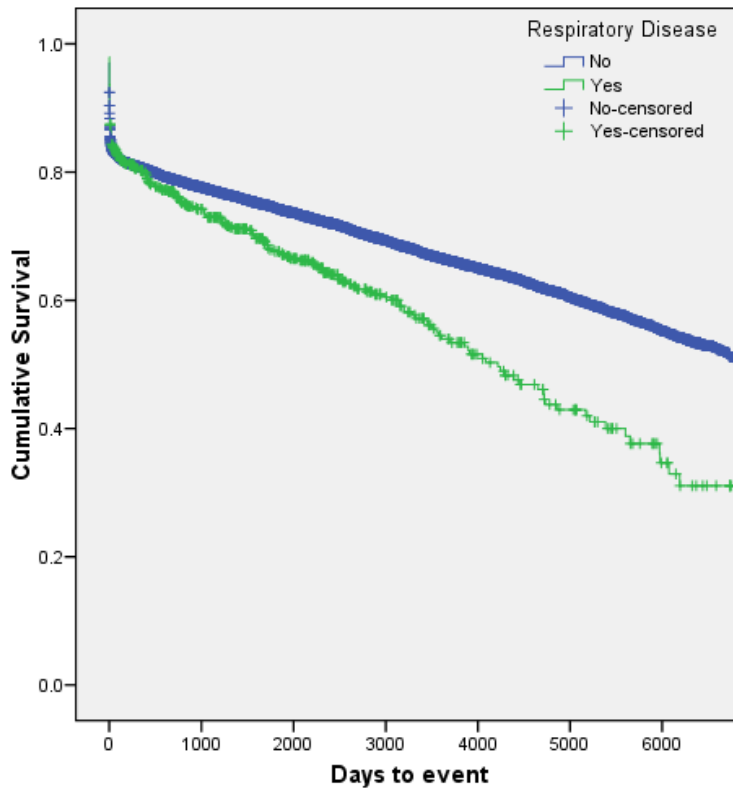


Figure 14 - plot for ages < 55 with and without respiratory comorbidity

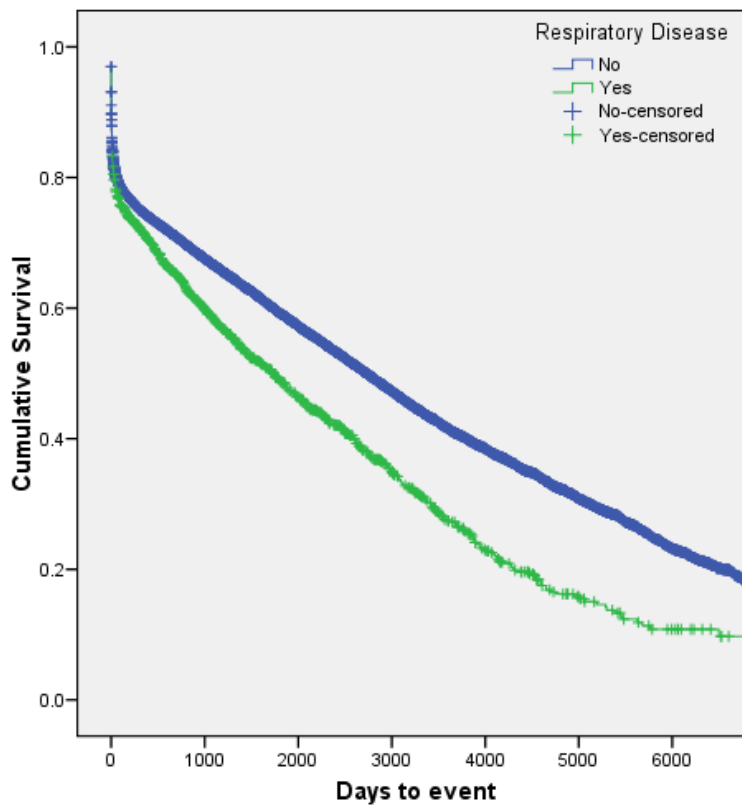


Figure 15 - plot for ages 55-64 with and without respiratory comorbidity

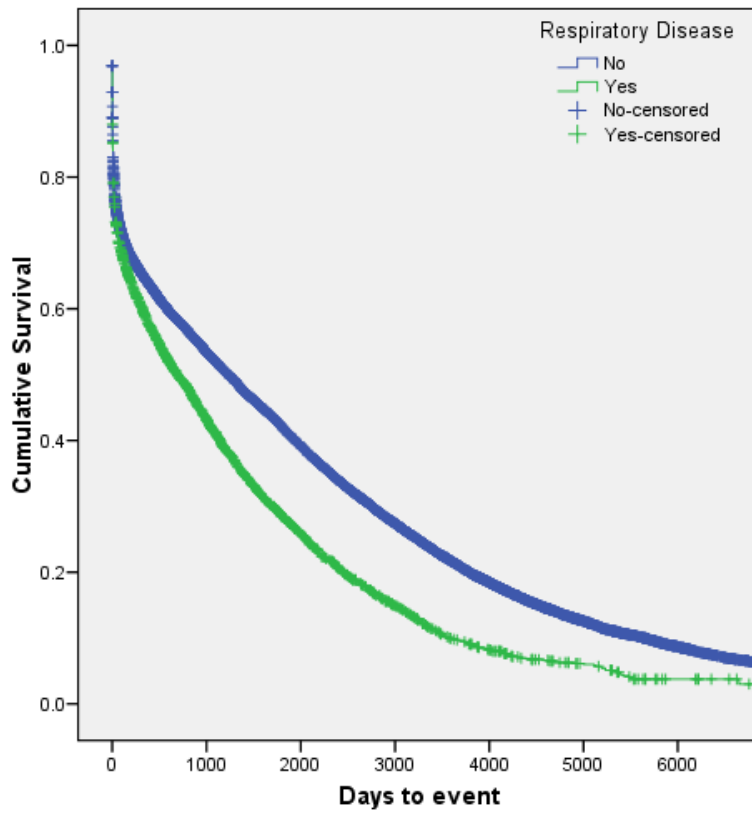


Figure 16 - plot for ages 65-74 with and without respiratory comorbidity

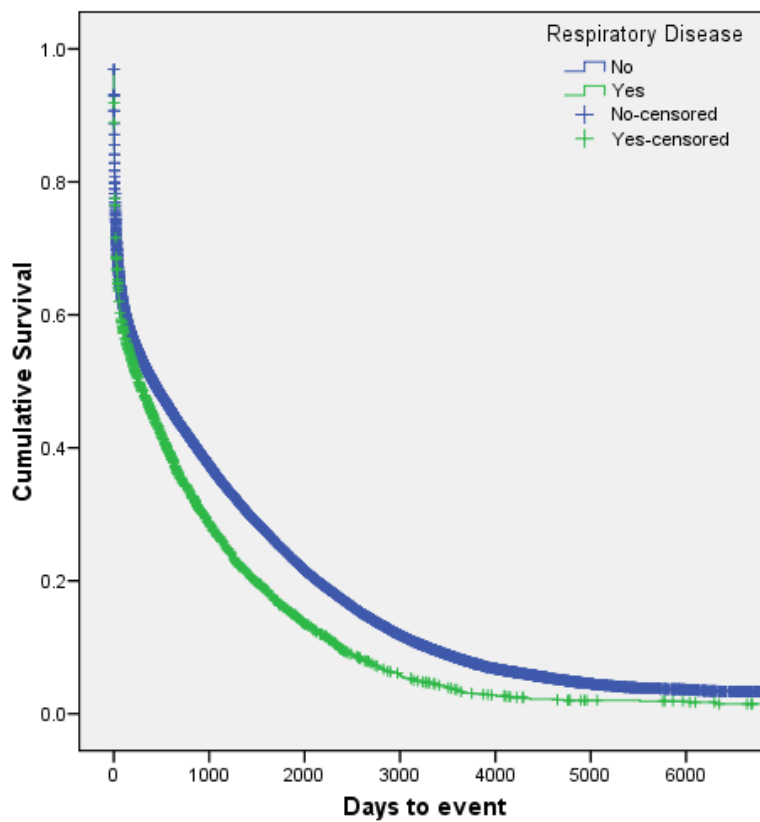


Figure 17 - plot for ages 75-84 with and without respiratory comorbidity



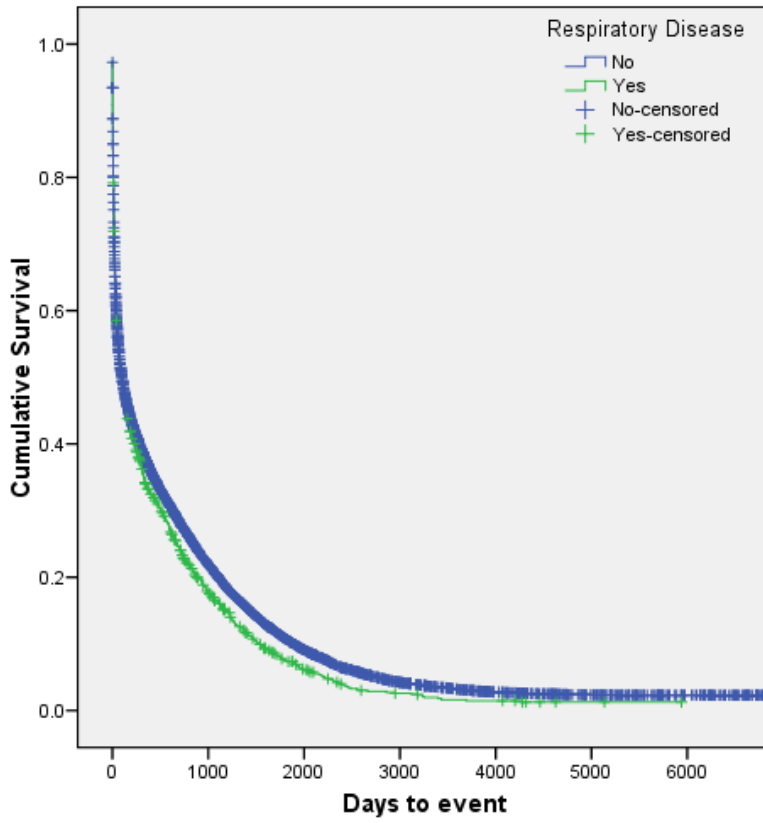


Figure 18 - plot for ages over 85 with and without respiratory comorbidity

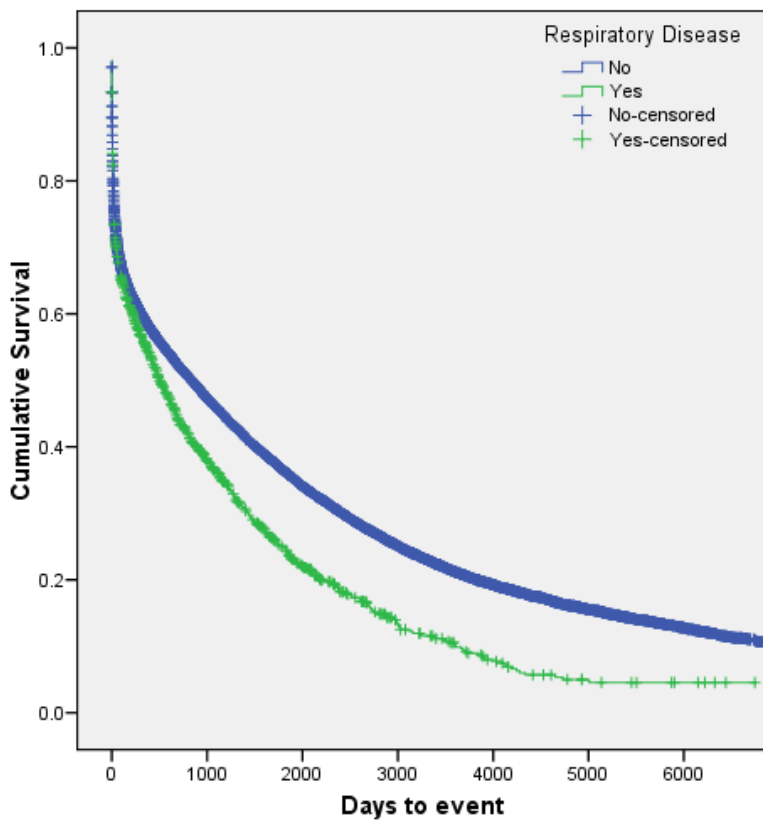


Figure 19 - plot for patients in deprivation category 1 with and without respiratory comorbidity

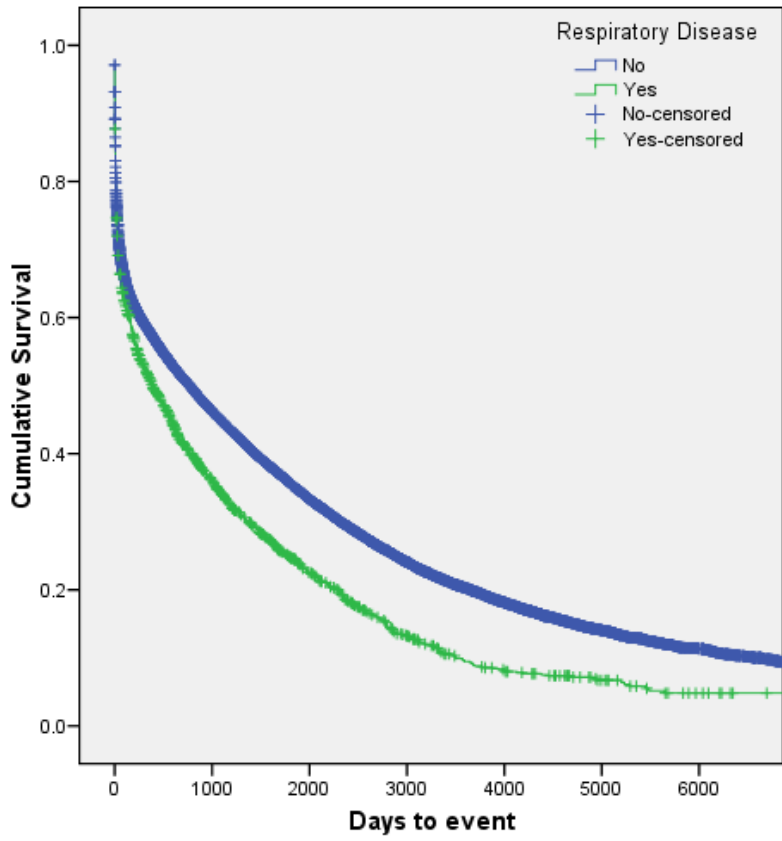


Figure 20 - plot for patients in deprivation category 2 with and without respiratory comorbidity

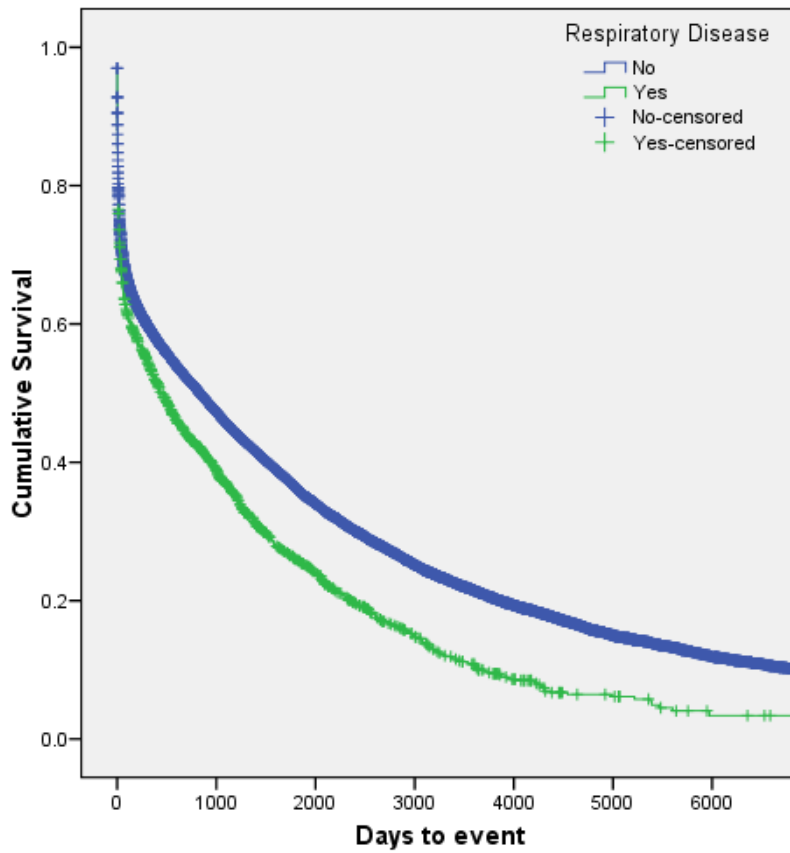


Figure 21 - plot for patients in deprivation category 3 with and without respiratory comorbidity

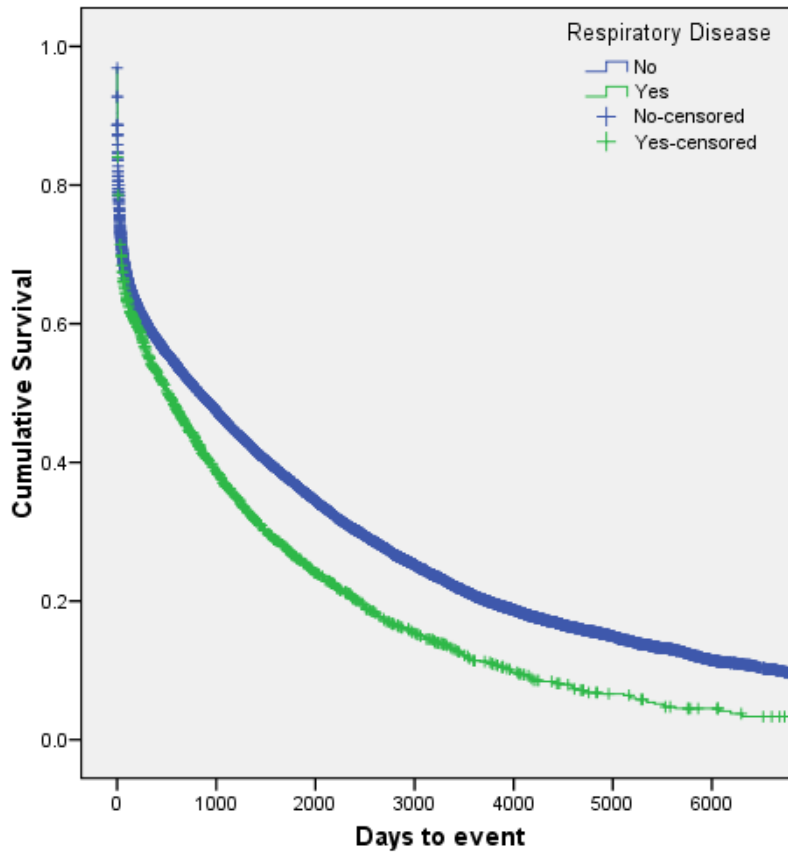


Figure 22 - plot for patients in deprivation category 4 with and without respiratory comorbidity

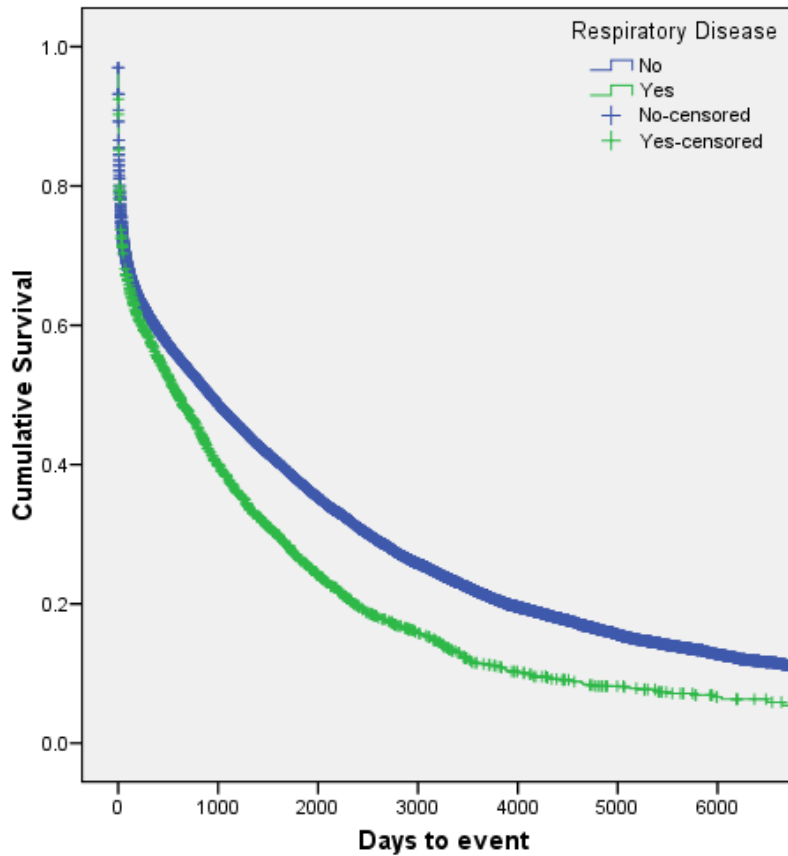


Figure 23 - plot for patients in deprivation category 5 with and without respiratory comorbidity

## KM plots by stroke subtype

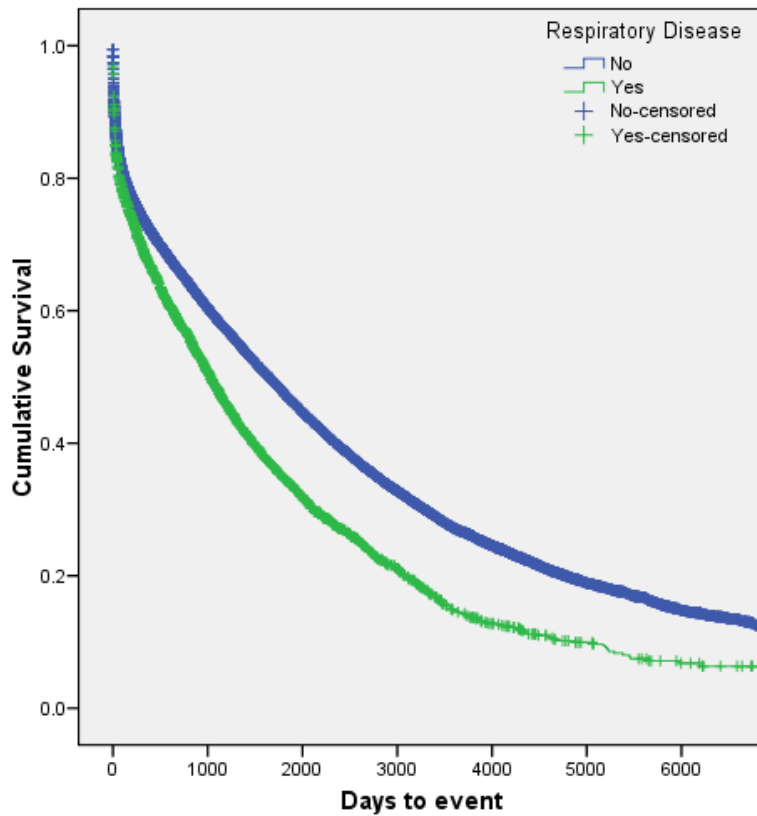


Figure 24 - plot for cranial infarction stroke subtype with and without respiratory comorbidity

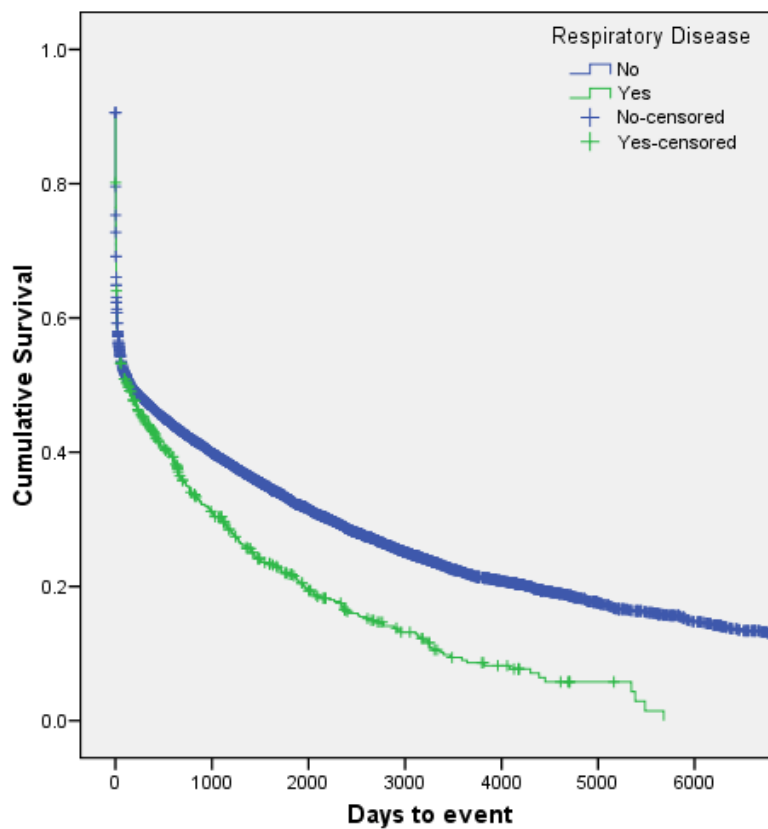


Figure 25 - plot for intracranial haemorrhage stroke subtype with and without respiratory comorbidity

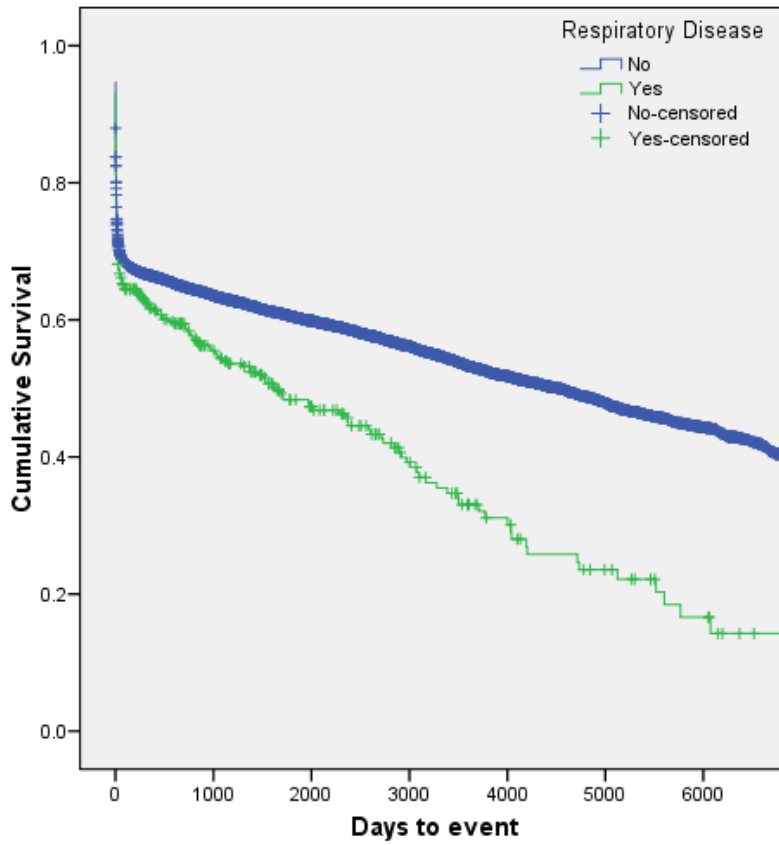


Figure 26 - plot for subarachnoid haemorrhage stroke subtype with and without respiratory comorbidity

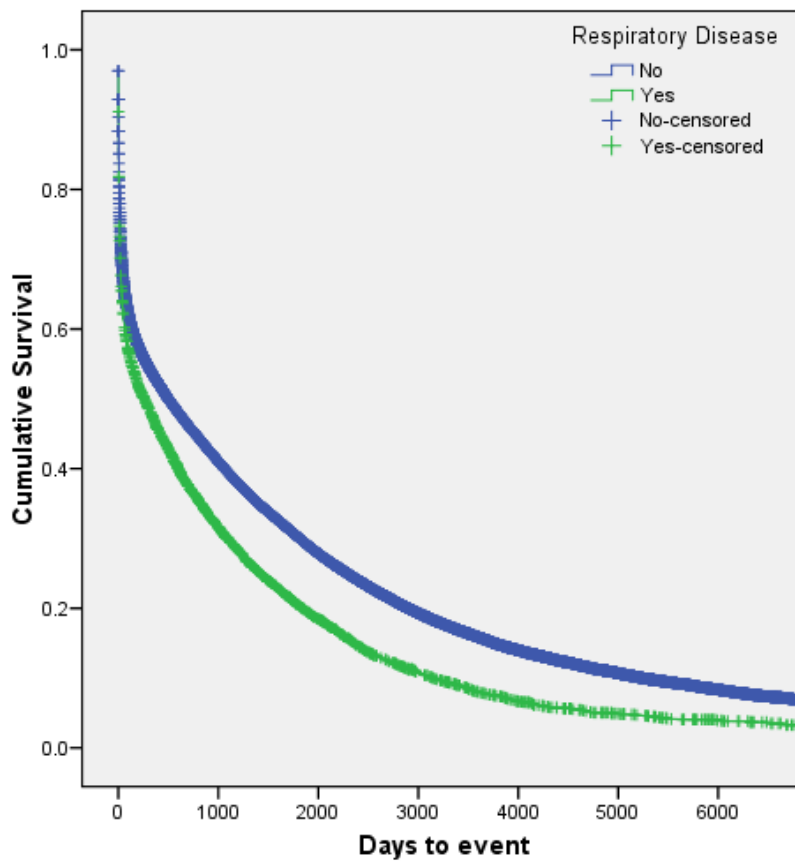


Figure 27 - plot for undefined stroke subtype with and without respiratory comorbidity

The preceding four KM curves show survival for the two groups separated by stroke subtype. The survival difference is most striking for subarachnoid haemorrhage with median survival for individuals with no respiratory comorbidity at 4543 days (95% CI 4257 to 4829) and for those with respiratory comorbidity 1627 days (95% CI 909 to 2345). The median survival data is tabulated in Table 24. Table 25 shows the median survival and log rank test data by stroke subtype.

		Median survival (days (95% CI))			Log rank (by respiratory)
		All	Respiratory comorbidity		
			No	Yes	
	All	818 (803 to 833)	851 (835 to 867)	501 (466 to 536)	p < 0.001
Sex	Male	1051 (1027 to 1075)	1119 (1093 to 1145)	517 (471 to 563)	p < 0.001
	Female	630 (611 to 649)	644 (624 to 664)	490 (436 to 544)	p < 0.001
Age category	<55	6870 (6687 to 7053)	6917 (6727 to 7107)	4217 (3574 to 4860)	p < 0.001
	55-64	2662 (2590 to 2734)	2732 (2657 to 2807)	1735 (1525 to 1945)	p < 0.001
	65-74	1162 (1130 to 1194)	1226 (1191 to 1261)	691 (618 to 764)	p < 0.001
	75-84	398 (382 to 414)	413 (396 to 430)	259 (219 to 299)	p < 0.001
	85+	98 (91 to 105)	99 (92 to 106)	85 (64 to 106)	p < 0.001
Deprivation quintile	1	808 (772 to 844)	839 (801 to 877)	503 (419 to 587)	p < 0.001
	2	732 (700 to 764)	770 (735 to 805)	384 (307 to 461)	p < 0.001
	3	803 (769 to 837)	834 (798 to 870)	450 (370 to 530)	p < 0.001
	4	798 (765 to 831)	837 (802 to 872)	510 (433 to 587)	p < 0.001
	5	883 (851 to 915)	920 (886 to 954)	597 (526 to 668)	p < 0.001

**Table 24 - Median survival times and log rank tests**

The pattern of greatly decreased survival with increasing age is shown clearly here. For all analyses, the survival difference between those with and without respiratory comorbidity is significant by the log rank test (p-value <0.001). The group surviving longest is the under 55 year olds with no respiratory comorbidity (6917 days (95% CI 6727 to 7107)) and the group with the shortest survival is those aged 85 and over (85 days (95% CI 64 to 106)). There is again no consistent pattern of differences in survival between least to most deprived quintiles. For the stroke type data in Table 25 - Median survival by stroke type, the least survivable stroke is intracranial haemorrhage 155 days (95% CI 116 to 194) and the longest survival is seen with subarachnoid haemorrhage 4322 days (95% CI 4054 to 4610). Cranial infarction has the second longest survival and “other” or undefined stroke type has the third longest.

		Median survival (days (95% CI))			Log rank (by respiratory)
		All	Respiratory comorbidity		
			No	Yes	
Stroke type	SAH	4322 (4054 to 4610)	4543 (4257 to 4829)	1627 (909 to 2345)	p < 0.001
	ICH	155 (116 to 194)	157 (115 to 199)	128 (38 to 218)	p < 0.001
	CI	1574 (1541 to 1607)	1646 (1611 to 1681)	1031 (963 to 1099)	p < 0.001
	Other	478 (463 to 493)	499 (483 to 515)	261 (225 to 297)	p < 0.001

**Table 25 - Median survival by stroke type**

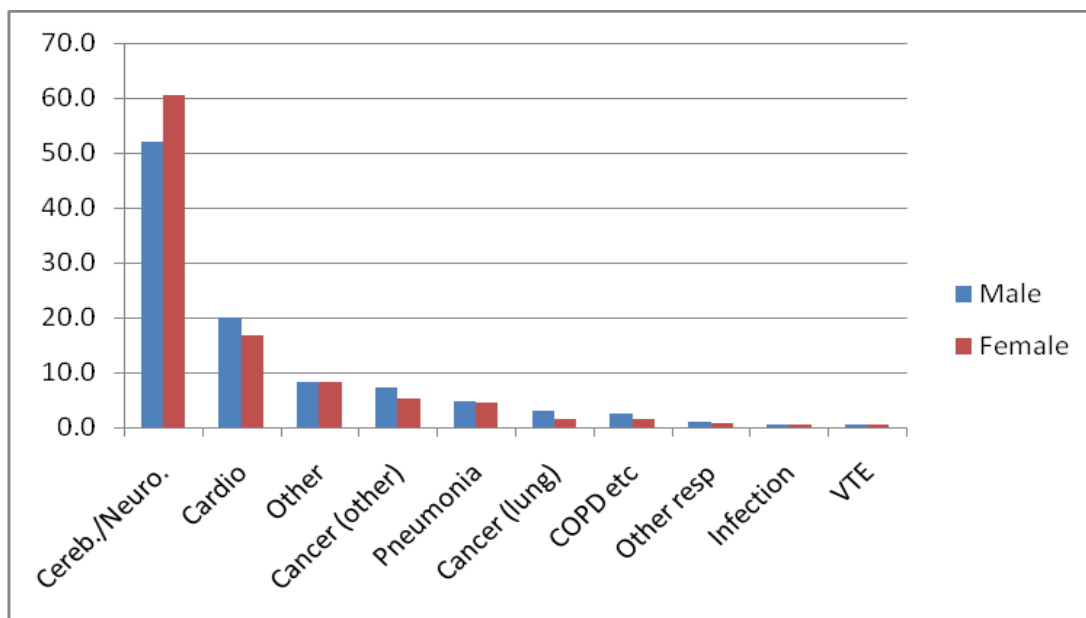
## Cause of death

### *All stroke patients*

Table 26 provides the proportions of modes of death for all the stroke patients by sex. By far the most common cause of death certified was stroke itself or the neurological sequelae at 56.9% overall. Cardiovascular death (such as MI) was second most common at 18.2%. Pneumonias make up only 4.6% of deaths with chronic respiratory diseases accounting for only 1.9%. Other causes of death contribute only a minor proportion of the total and the percentages are very similar between sexes. These data are illustrated graphically in Figure 28.

	Male n (%)		Female		Total	
Cerebrovascular/Neurological	25921	(52.0)	39953	(60.6)	65874	(56.9)
Cardiovascular	10033	(20.1)	10997	(16.7)	21030	(18.2)
Other	4084	(8.2)	5476	(8.3)	9560	(8.3)
Cancer (other)	3647	(7.3)	3404	(5.2)	7051	(6.1)
Pneumonia	2367	(4.7)	2924	(4.4)	5291	(4.6)
Cancer (lung)	1527	(3.1)	967	(1.5)	2494	(2.2)
COPD/Asthma/Bronchiectasis	1249	(2.5)	960	(1.5)	2209	(1.9)
Other respiratory	560	(1.1)	570	(0.9)	1130	(1.0)
Infection	264	(0.5)	302	(0.5)	566	(0.5)
Venous thromboembolism	223	(0.4)	351	(0.5)	574	(0.5)

**Table 26 - primary cause of death in stroke patients**



**Figure 28 - proportion (%) of primary cause of death amongst males and females with stroke** (cereb/neuro = cerebrovascular/neurovascular, cardio = cardiovascular, COPD etc = COPD, asthma & bronchiectasis, VTE = venous thromboembolism)

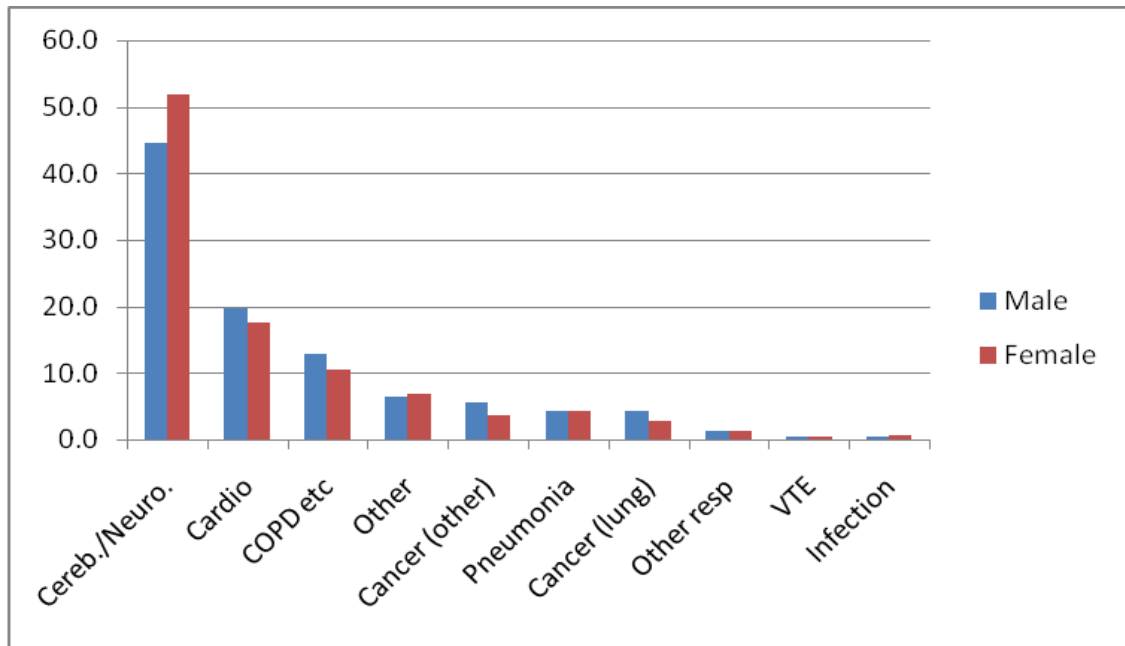
### ***Stroke patients with prior respiratory comorbidity***

Death certification figures for the stroke patients with respiratory comorbidity are shown in Table 27 - primary cause of death in stroke patients with respiratory comorbidity. Stroke and neurological sequelae was the most common cause of death for both sexes (44.6% males, 51.8% females and 48.1% overall) and cardiovascular causes was the second most common cause (19.8% males, 17.6% females and 18.7% overall). Chronic respiratory diseases contribute as the third most common cause of death in this group at 11.7% overall, 12.9% for men and 10.5% for women. Pneumonia, cancer, venous thromboembolism, infections and other causes contribute only minor percentages. Figure 29 presents these figures as a bar chart.

	Male		Female		Total	
Cerebrovascular/Neurological	1950	(44.6)	2138	(51.8)	4088	(48.1)
Cardiovascular	865	(19.8)	724	(17.6)	1589	(18.7)
COPD/Asthma/Bronchiectasis	563	(12.9)	434	(10.5)	997	(11.7)
Other	285	(6.5)	286	(6.9)	571	(6.7)
Cancer (other)	248	(5.7)	150	(3.6)	398	(4.7)
Pneumonia	186	(4.3)	180	(4.4)	366	(4.3)
Cancer (lung)	186	(4.3)	115	(2.8)	301	(3.5)
Other respiratory	54	(1.2)	51	(1.2)	105	(1.2)
Venous thromboembolism	22	(0.5)	22	(0.5)	44	(0.5)
Infection	16	(0.4)	25	(0.6)	41	(0.5)

**Table 27 - primary cause of death in stroke patients with respiratory comorbidity**





**Figure 29 - proportion (%) of primary cause of death amongst males and females with stroke and respiratory comorbidity (cereb/neuro = cerebrovascular/neurovascular, cardio = cardiovascular, COPD etc = COPD, asthma & bronchiectasis, VTE = venous thromboembolism)**

## 6. DISCUSSION

Stroke is clearly a common disorder in Scotland and its crude incidence has changed little over the period 1985 to 2005. Comorbidities are also common with one or more being present in 58.1% of patients. COPD and other chronic lower respiratory diseases are also highly prevalent in Scotland and responsible for great mortality in their own right. The specific effects of COPD or other respiratory diseases on stroke outcome were not examined by any of the studies found in the literature search. The results of this study cannot, therefore, be directly compared to any other.

### Incidence rates

The male and female crude incidence levels show a relatively small variation from 1985 to 2005. There is a small rise until 1993 and a gradual fall in incidence thereafter. The standardised figures however show a rise in incidence until 1992 followed by a gradual reduction in incidence until 2005. In 2005, the standardised incidence rates for both sexes are lower than in 1985. The figures are comparable to those from the Scottish Borders Stroke Study<sup>117</sup>. World standardised rates per 100000 in the SBSS were 71 for infarction and 8 for haemorrhage, compared with 61.4 to 80.7 from the SMR data. The rate standardised to the Scottish population in the SBSS was 161 per 100000 (compared with 137 to 169 from SMR data). It may not be unreasonable to assume that most strokes would be admitted to hospital (and thus appear in the SMR database), but this may not necessarily be the case. It is feasible that mild strokes (especially in areas far removed from hospitals) may have been managed at home. It may also be possible that severe or imminently fatal strokes may also have been managed at home (for example in a nursing home). With the recommendations of the Stroke Unit Trialists' Collaboration<sup>118</sup>, there may have been an increased tendency for stroke patients to be admitted to hospital in the second decade of the study period. It would certainly seem unlikely that there would be a decreasing tendency for stroke admissions. If this is the case, then the reduction in standardised figures may be due to improved primary prevention strategies in Scotland. Improved recognition of diabetes, hypertension and other cardiovascular risk factors could feasibly lead to an improvement in stroke figures. Over the period studied, there has been a large increase in available evidence based guidelines for recognition and management of these risk factors. Primary care practitioners have been encouraged to target these risk factors. Specific reasons for the trends seen in incidence cannot be ascertained from the information in this study and can only be speculated upon.

## **Baseline characteristics**

### ***Sex and age groups***

For both sexes, the age distribution exhibits negative skew in a normal distribution. This is unsurprising given the wealth of data showing age as a strong risk factor for stroke. The skew is stronger for females in that there are many more very elderly females having strokes than men. For instance, in the 75 to 84 years group, there are over 10000 more women than men. Women of course live longer than men in general, which would account for this difference. The median age of women was 5 years older than the men in the group. This is comparable to other studies of stroke, the largest age difference being in the PISCIS<sup>47</sup> project where the mean female age was 7.3 years older than for males.

### ***Deprivation categories***

There are a greater number of strokes with each category of increasing deprivation, which agrees with other studies documenting this<sup>119-121</sup>. Risk factors, such as tobacco smoking<sup>122</sup> and poor health in general<sup>123</sup>, are known to be more prevalent in more deprived areas which likely explains the bulk of this effect. This gradient effect is very similar for both men and women. Age subgroup analysis also shows this clearly for both sexes under the age of 74. In the older age groups, the effect is less so. In the 75 to 84 year olds, the effect is fairly uniform but over the age of 85 there appears to be a reverse gradient. There appear to be more strokes in the least deprived quintiles and fewer in the most deprived. This was also seen in the Avendano paper<sup>120</sup>. The reason for this is not clear, however a possible explanation from the Smits<sup>119</sup> paper may also apply to Scotland. There is a possibility of selection bias. As the deprivation data is derived from postcodes, patients from different areas may have a higher or lower chance of being admitted or dying before admission. This could explain the effect. It is feasible that very elderly patients from deprived areas may have more chance of dying from the first stroke and thus not be admitted. Those from less deprived areas may have less comorbidity associated with socioeconomic status and survive until admission. This could lead to an underestimation of the true incidence in very deprived, very elderly persons. Avendano *et al* suggest a survival effect. This is the theory that individuals in lower socioeconomic groups may die younger from other causes leaving only the healthiest to live into old age. Also, those in lower deprivation groups may live longer and thus have a stroke at a very old age causing an apparent reversal of the gradient. Other factors such as race and genetic susceptibility may be important but data regarding this is not present in this study and cannot therefore be commented upon.

## **Comorbid conditions**

Well over half of both sexes had at least one comorbid condition at the time of first stroke. The commonest occurring were hypertension and ischaemic heart disease. Hypertension is a well known risk factor for stroke and ischaemic heart disease shares risk factors so this is not unexpected. Comorbidity data from studies examined in the literature search are broadly comparable to these figures. Hypertension, however, was more often present at over 50%. The data from the SMR therefore is far lower than might be expected. Two scenarios may explain this. Either hypertension is truly less prevalent or is less well recognized. The implications from the latter scenario would be under-treatment of an important risk factor in this population. Definitions of hypertension have also changed over the study period, so data from the early years may not be directly comparable to the later years. Diabetes and atrial fibrillation are also risk factors in the aetiology of stroke and occur commonly in this population. Heart failure and respiratory disease were the next most commonly occurring conditions. Heart failure also shares risk factors with stroke (smoking, hypertension) but the relationship with respiratory disease is not as obvious. There is certainly a link between respiratory disease and stroke (as discussed earlier in this thesis), but it is far from clear. These data provides no insight into causative links, but the fact that respiratory diseases are fairly common in the stroke population is in itself interesting.

## **Stroke subtype**

The majority of strokes for both sexes fall into the undefined category. This is far more than in other studies. OCSF reported 5% as unknown pathological type and most (81%) were infarction. The majority of other stroke studies including subtype data have similar figures with few unspecified types, few haemorrhages and mostly infarction. This could represent coding inaccuracies where there is no other information other than “stroke” present. Two studies do give similar results. Brønnum-Hansen<sup>109</sup> *et al* found unspecified stroke in 54.7% and the Copenhagen City Heart Study<sup>124</sup> had a similar proportion of 53%. These studies used a register or coded discharge data. This is likely more akin to the SMR data than many of the other papers which often had neurologists or the trial physician following up or even examining the cases. Two scenarios may explain the high proportion of unspecified stroke in the SMR data. There may be a decision not to CT scan a patient who is clearly going to die (when the scan would not change management, but would have otherwise defined the stroke as infarction or haemorrhage). Also a patient with mild or unclear signs with unclear results on CT scanning may be placed in this category. This

may have been more likely at the beginning of the study when CT scanners were either unavailable in many hospitals or of low resolution due to the technology available. It is far less likely that this would happen in the latter years given widespread availability of scanners and the increased resolution. The majority of these unspecified strokes are likely to be ischaemic (which is the next most common category), as demonstrated in most studies of stroke subtype. It would appear that when cases are followed up by experts, the number of strokes labeled as “unclassified” decreases.

## **Stroke patients with COPD and other chronic lower respiratory diseases**

### ***Prevalence***

Respiratory diseases were present in 6.9% of the stroke population studied. More men (7.7%) than women (6.2%) had documented respiratory disease. A greater proportion of men than women are known to be smokers in Scotland<sup>125</sup>, which may explain this statistic. This is similar to data from other papers from 5.8%<sup>62</sup> to 15.3%<sup>85</sup>. A study of stroke admissions in Glasgow<sup>66</sup> reports COPD as a comorbid condition in 10.2%. This is slightly higher than reported in this thesis for the whole of Scotland, especially as asthma and bronchiectasis are also included. This may relate to the very high levels of smoking in the Glasgow area<sup>125</sup>.

### ***Sex and age groups***

The mean ages and distribution across the percentiles are very similar for the subgroup with respiratory diseases when compared to the main study population. However, in all stroke patients there was a slight difference in age between sexes with women marginally older than men. In the respiratory cohort, this difference is no longer evident. The reason for men in this group being slightly older is unclear. There are likely to be more smokers in this group so it could be postulated that there may be a selection bias. Smoking and respiratory comorbidity may cause an earlier death from cardiac or respiratory causes, therefore selecting the “fitter” patients to survive to a later age and then have their stroke. As males have more cardiovascular disease than women in general, there may be fewer males living long enough to have a stroke, hence the mean age is higher.

### ***Deprivation categories***

The distribution of numbers of stroke patients with respiratory comorbidity within the deprivation categories is very similar to the whole stroke population. The socioeconomic

gradient does appear to be more striking, however. For both males and females, there is a greater proportion of the cohort in the more deprived Carstairs deprivation quintiles. This may be an effect of smoking which is likely to be more prevalent in the group of individuals with respiratory disease and also more prevalent with decreasing socioeconomic status.

### ***Comorbidities***

In general, a greater proportion of the subgroup of patients with respiratory disease has each of the listed comorbidities in comparison to the whole population. The difference is most impressive for the vascular comorbidities. 19.3% had heart failure, compared with 7.7% of the stroke patients. 34.2% had ischaemic heart disease (compared with 17.6%) and hypertension is similarly higher. Although without direct evidence from this study, it is probably safe to assume that a larger proportion of this subgroup are smokers than in the whole study population. If this is true, then the well known links between cigarette smoking and cardiovascular and cerebrovascular disease could explain the large differences between the two groups. The growing evidence on poor respiratory function as a risk factor for atherogenesis and vascular disease (independent of smoking history), as detailed earlier in this thesis, may also be an explanation for this observation.

### ***Stroke subtype***

There are fewer subarachnoid haemorrhages and marginally more ischaemic strokes than in the whole group. When analysed by age group, the respiratory group appears to have proportionally more cerebral infarction and “other” strokes within the younger age groups. The reason for this is not clear from the data available. One theory is that, due to the higher levels of comorbidity in this group, fewer patients survive to an old age in order to have the stroke (by dying from another condition). This would mean a larger proportion of younger individuals left alive to have a stroke. Alternatively, respiratory disease or an associated risk factor (e.g. smoking) may predispose to stroke at a younger age.

## **Survival**

### ***Overall***

The survival rates to 30 days and 1 year for Scottish stroke patients are very similar to the rates observed in other stroke studies and lie around the middle of these other observed rates. They are most similar to the studies undertaken in Western countries, although lower than two American studies (North Carolina<sup>86</sup> had a 30 day survival rate of 95% in

1980 and GCNKSS<sup>95</sup> had 85.3% in 1999). It is encouraging that these figures are in line with those of similar countries. There is an increase in the crude mortality from 1995 until 1999. This could be due to the effect of an ageing population. There follows a reduction in mortality. When standardized to European or World populations to account for this, there is a more modest increase prior to the reduction. There may be multiple reasons for the change. Numminen *et al*<sup>106</sup> found a decrease in severity of stroke which may have accounted partly for the decrease in mortality. There has been a decrease in the incidence of stroke over the study period. Truelsen *et al*<sup>124</sup> also reported that a fall in incidence was an important factor. Stroke care has improved, as has recognition and treatment of risk factors. Treatment of other comorbidities has also improved, which may have helped reduce mortality after stroke from other causes. Barker *et al* in Portland<sup>72</sup> also saw a decline in mortality. A corresponding fall in the prevalence of hypertensive heart disease was also seen. It was postulated that this equated to better treatment of mutual risk factors for stroke and heart disease. This could also be the case in the Scottish population. More rapid access to hospitals with CT scanners and therefore faster diagnosis and management of acute stroke plus the immediate aftercare could also be a reason for improved mortality. Howard *et al*<sup>86</sup> saw in particular an increase in survival from ICH and SAH. They also thought that better control of risk factors was likely a factor but that better diagnosis may have led to the inclusion of less severe strokes with a better outcome, thus reducing the overall mortality. Thrombolysis for stroke is a relatively recent addition to most Scottish hospitals may be of some influence in these figures, but most likely only in the last few years of the study.

### ***Short term survival***

Short term survival from stroke is poor. In Scotland, it is similar to figures from other studies, in particular those from the Western World. It is not as high as the survival rates in Oxfordshire<sup>105</sup> (81%) but was greater than the rate in Kolkata<sup>100</sup>. This may be due to differences in comorbidities or stroke aftercare. Das *et al* thought that poor immediate care of stroke was responsible for the high case fatality rate in India. Stroke care in Scotland and Oxfordshire are likely to be similar, but better care and stroke units may have been introduced earlier in Oxfordshire. In a review of Scotland's stroke services, Dennis<sup>126</sup> states there were very few stroke units around 1993, but the number has greatly increased since. A quarter of all patients were dead at 30 days. This is worse with increasing age – over a third of those aged over 85 were dead at 30 days. Survival is also consistently worse in women than men. This is in line with findings from other studies. The gender difference is likely due to the higher proportion of women in the older age groups.

Interestingly, there is little variation in mortality across the deprivation quintiles. This would suggest that hospital care is a more important determinant of survival than social background.

The type of stroke associated with poorest survival is intracranial haemorrhage. Those with cranial infarction had the most favourable survival rates. Subarachnoid haemorrhage was also associated with a higher survival rate (although still poor at 72.7% for men and 69.9% for women). This probably reflects the younger age of these patients who most likely had few comorbidities. These rates are similar to those reported in Perth<sup>55</sup> (60% in 1990 and 75% in 2001) and the GCNKSS<sup>95</sup> (62.8% in 1994 and 68.7% in 1999). Many of the other studies reviewed had much lower survival rates for SAH (48% in 1969, Rochester, 54% in 1981, Framingham and 55% in 1986, Oxfordshire). These studies were all performed much earlier than the data in this paper and are therefore not directly comparable. Diagnosis, treatment and aftercare of SAH have changed over this period. It likely reflects an increased ability to pick up and treat SAH at an earlier stage, thus increasing survivability. Survival rates in Finland<sup>98</sup> over a similar time period are still poor (46.2% for SAH in 1991) despite increased treatment of risk factors and improved care. The undefined “other” stroke type had a similar survival rate to SAH and CI. This category may incorporate patients with a clinical diagnosis of stroke but vague neurology and equivocal CT (most likely infarction), patients arriving in a moribund state where further classification is not possible (or helpful clinically) and CT may not be performed and patients who may not have had stroke. The balance is probably toward those with mild infarcts as an excess of moribund patients would have put the survival figure closer to that of ICH. Studies with a stringent follow-up of patients such as Oxfordshire<sup>50:105</sup> had a much lower survival rate for this category of stroke (26%). This may mean that milder strokes with a more favourable outcome were more accurately diagnosed as infarction. Thus the unclassified group would be more likely to consist of moribund patients where clinical state may have made accurate diagnosis either more difficult (due to speed of decline) or clinically unhelpful (if a patient would be for palliative care in any event).

### ***Long term survival***

Survival at 1 and 5 years is very poor. This is again very similar to reports from other studies. The lowest survival was 48% in Moscow<sup>99</sup> and the highest 65.9% in Finland<sup>98</sup>. Overall, just over half (58.1%) are alive at 1 year and just over a third (35.2%) at 5 years. This is again worse in females than males. The age gradient is much more pronounced than at 30 days. At 1 year 80.2% of under 55 year olds were alive but only 36.6% of the



over 85s. This means that those under 55 had more than twice the likelihood of being alive at 1 year than the over 85s. At 5 years, the under 55s were more than 6 times likelier to survive than the over 85s. Some of this may be explained by better general fitness and less comorbidity in the young. However, the probability of death from any cause must increase with increasing age in the general population. An elderly survivor of first stroke is in general less likely than a 55 year old to survive the next 1 or 5 years for a myriad of reasons related to age. As at 30 days, there is little variation with survival at 1 and 5 years across deprivation categories.

### ***Survival with comorbid conditions***

Patients with any one or more comorbidities had similar survival rates at 30 days. At 1 and 5 years, the two groups diverge so that having any comorbidity is associated with worse survival. It seems logical that having no comorbidity is beneficial to longer term survival. Those with diabetes and hypertension had some of the higher 30-day, 1 and 5 year survival times. These are recognized risk factors for vascular disease. It may be that the treatment of these diseases led to less severe strokes. The converse of this could be that the other categories included people with unrecognized and therefore untreated diabetes and hypertension, leading to more severe strokes. Cancer, heart failure and renal failure carried the worst survival rates at 30 days, 1 and 5 years. This is unsurprising given the poor outcomes from these diseases in general

## **The effect of chronic lower respiratory tract diseases on survival of stroke patients**

Chronic lower respiratory tract diseases were associated with poorer survival following first stroke. This is still evident when analysis of age groups, deprivation categories and stroke subtype is performed. Women have poorer survival at 30 days, but the difference in survival between men and women is less at 1 year and there may even be a tendency for greater survival in women at 5 years (although there is some overlapping of confidence intervals). The Kaplan-Meier curves show a rapid divergence in survival with respiratory disease consistently associated with a poorer outcome. This difference is maintained for the period of follow up in all subgroup analyses, but is less obvious with increasing age. Median survival time is statistically different (log rank (by respiratory) p value < 0.001) for all subgroups. The mean age of males was higher than in the whole study cohort and there was no difference in mean age between the sexes (as there was in the whole cohort with males being younger). There are fewer patients in the very young age groups (less than 55

and 55-64) than in the whole study population. There are also fewer patients in deprivation categories 1 and 2. A large proportion of the respiratory disorders are likely to be COPD. It is accepted that the vast majority of people need a 20 pack year smoking history (that is, smoking 20 cigarettes a day for 20 years) to develop the disease. Therefore it is expected that fewer people would develop it at a younger age. Younger age was associated with a better outcome in the whole stroke population, so the smaller proportion of younger patients in the respiratory subgroup may partly account for an overall poorer survival. Also, having fewer individuals in the least deprived socioeconomic groups may have some contributions. The burden of smoking is likely to be greater in poorer socioeconomic class. Deprivation and smoking most likely contributes to greater comorbidity in these patients. The proportion of ischaemic heart disease, hypertension, heart failure and atrial fibrillation is certainly higher in this group. IHD was present in 19.4% of the whole stroke population, but was much higher in the respiratory group at 35.9%. Analysis of cause of death, however, does not show any differences between the whole stroke population and the respiratory subgroup. Cerebrovascular causes primarily lead to death in both groups studied, at roughly the same proportions. There is no increase in the proportion of cardiovascular deaths seen in the respiratory group, nor is there a difference in pneumonia as a cause of death. A greater proportion of those in the respiratory group die of respiratory causes (11.7%) compared with the whole group (1.9%). This reflects an expected greater morbidity from respiratory causes in people already diagnosed with a respiratory condition. Although this accounts for some of the differences in survival, it is still a relatively small proportion of the total deaths and a cerebrovascular cause is by far the most common, accounting for nearly half. There must therefore be other factors involved. The proportions of stroke types in the whole group and the respiratory group are similar, but stroke severity cannot be ascertained from this data. If this group of patients had more severe strokes within each category, it could contribute to poorer survival, but this is just conjecture and would have to be studied further. As discussed earlier in this thesis, respiratory disease is associated with excess cardiovascular risk and it may be that there are an excess of cardiovascular deaths in the respiratory group. Death from MI, for instance, may be fairly sudden and have few signs to enable the certifying doctor to label it as such. If the decedent was known to have had a recent stroke, death may be certified as stroke in the absence another obvious cause. Physician accuracy of determining cause of death from stroke<sup>127</sup> or cardiac<sup>128</sup> causes can be unreliable and of varying accuracy. Studies have compared death certificate cause of death with autopsy findings and have shown substantial differences<sup>129</sup>. The reliability of the documented causes of death cannot be confirmed or refuted from the data in this study. A further investigation into accuracy

of death certification would need to be undertaken. Data from necropsies would be most helpful to ascertain accurate cause of death, but unfortunately postmortem rates were falling through the study period and have continued to decline in the United Kingdom<sup>130;131</sup>. Also of particular interest in examining the age groups, the very young (less than 55) with respiratory comorbidity have a median survival time that is 2700 days less than for the whole cohort. This difference is lessened with each increasing age group meaning the adverse survival effect is maximal in the under 55s. This potentially has huge implications. If survival in this group is so poor, perhaps extra attention should be paid to primary stroke prevention in young patients with respiratory disorders, especially COPD. Of course all patients following stroke should have vigorous attention to secondary prevention, but the presence of comorbidities (especially respiratory) should prompt the treating physician to be aware that survival is likely to be less favourable. Thus, extra vigilance regarding treatment of cardiovascular risk factors is needed.

## **Strengths and weaknesses of the study**

A study of this nature can only suggest a relationship between factors and unfortunately cannot ascertain causality. It would be interesting to know whether the group with respiratory disease had worse strokes than the whole cohort. This would involve examining admission data such as the National Institute of Health Stroke Scale (NIHSS). This is not feasible for a retrospective study of this size and the data is probably not available for many of the cases, especially for data towards the beginning of the study period where records may have been destroyed. A study of different design would have to be devised. Although strokes are reasonably likely to be admitted, milder strokes may not have been and TIAs are usually only admitted in certain circumstances. The data may therefore be lacking milder forms of stroke disease, which could affect the analysis. It may be important to know how respiratory comorbidities affect outcomes from milder stroke or TIA. Although main admission diagnosis is known to be fairly accurate<sup>114</sup>, secondary diagnoses are less so. Again, this could skew the analysis by omitting for example stable or mild forms of respiratory disease. There are likely to be many individuals with unrecognized disease who would therefore not have a respiratory comorbidity recorded. This is impossible to quantify. It would therefore be more accurate to perform a study where the lung function of each subject was known (although simple spirometry is also inherently variable both demographically speaking and is effort dependent). Smoking status data was not available for this study. Smoking is a well known risk factor for stroke and respiratory disease (COPD) and may have been a very big risk factor for adverse outcome. The respiratory group in the study probably contained more smokers; therefore

the ability to correct for this would have been useful. Despite these problems, the study did involve very large numbers of patients which may have helped increase the power of the study and keep the confidence intervals small. It would not be possible to collect very large amounts of data on each individual to suit the needs of every research question in a database of this size. Hopefully, however, a study such as this can help identify areas of potential concern for further, more detailed research.

## **Conclusions**

The incidence of stroke in Scotland has decreased since 1986, although this decrease has been more rapid since 1998.

A large proportion of stroke patients have one or other comorbidities.

Standardised mortality rates from stroke have fallen over the period 1995-2005, although crude rates have not.

Survival from stroke is poor, especially in the long term.

Survival in stroke patients with a respiratory condition is especially poor when compared to all stroke patients.

Survival in individuals with stroke aged less than 55 with a respiratory comorbidity is especially poor when compared to all individuals of the same age group.

Patients with respiratory comorbidity are still certified as dying from the same causes as all stroke patients, namely a cerebrovascular or cardiovascular cause.

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## 8. APPENDICES

Year	All ages			<55			55-64			65-74			75-84			85+		
	Total	Males	Females	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
1986	5111760	2462311	2649449	3814237	1918542	1895695	553951	260621	293330	434861	184430	250431	251916	86255	165661	56795	12463	44332
1987	5099020	2455403	2643617	3798202	1909765	1888437	548552	258216	290336	437669	186521	251148	254879	87768	167111	59718	13133	46585
1988	5077440	2444319	2633121	3775862	1897403	1878459	545007	257057	287950	436513	186613	249900	257477	89370	168107	62581	13876	48705
1989	5078190	2443165	2635025	3772358	1893100	1879258	542486	256233	286253	437374	188181	249193	260125	90915	169210	65847	14736	51111
1990	5081270	2443865	2637405	3776310	1892806	1883504	540044	255400	284644	437189	189081	248108	260368	91363	169005	67359	15215	52144
1991	5083330	2444515	2638815	3775995	1890986	1885009	536887	254254	282633	441094	191920	249174	259086	91372	167714	70268	15983	54285
1992	5085620	2445272	2640348	3776162	1889770	1886392	535665	253947	281718	445444	194316	251128	255857	90503	165354	72492	16736	55756
1993	5092460	2448419	2644041	3781035	1890794	1890241	536030	254628	281402	451300	197302	253998	249393	88264	161129	74702	17431	57271
1994	5102210	2453342	2648868	3789126	1893745	1895381	535792	254821	280971	457044	200385	256659	243592	86322	157270	76656	18069	58587
1995	5103690	2453353	2650337	3786530	1890437	1896093	535129	255067	280062	451264	198712	252552	251269	90110	161159	79498	19027	60471
1996	5092190	2447020	2645170	3775462	1883207	1892255	531712	253660	278052	447732	197778	249954	256208	92700	163508	81076	19675	61401
1997	5083340	2442322	2641018	3763038	1875333	1887705	531276	254056	277220	445955	197410	248545	260399	95143	165256	82672	20380	62292
1998	5077070	2438991	2638079	3747550	1865931	1881619	536941	257313	279628	445484	197891	247593	262317	96489	165828	84778	21367	63411
1999	5071950	2436535	2635415	3733737	1857221	1876516	543141	260969	282172	444420	198082	246338	264516	98260	166256	86136	22003	64133
2000	5062940	2431926	2631014	3717226	1846995	1870231	546229	263102	283127	445212	199064	246148	266612	100125	166487	87661	22640	65021
2001	5064200	2433733	2630467	3705330	1840422	1864908	551689	266601	285088	446642	200495	246147	271745	103167	168578	88794	23048	65746
2002	5054800	2431805	2622995	3668627	1823172	1845455	573294	277735	295559	448587	201954	246633	276287	105746	170541	88005	23198	64807
2003	5057400	2434566	2622834	3649719	1813456	1668803	588618	285594	303024	452266	204450	247816	280896	108235	172661	85901	22831	63070
2004	5078400	2446248	2632152	3648785	1812385	1836400	603061	293181	309880	455076	206596	248480	286232	111073	175159	85246	23013	62233
2005	5094800	2456109	2638691	3648451	1812217	1836234	613255	298599	314656	456697	208182	248515	285749	111781	85228	90648	25330	65318

Table 28 - General Register Office for Scotland mid year population estimates 1986-2005

Study	Location (n)	Study type	Period	Incidence		
				Men	Women	Total
PCSS <sup>55</sup>	Perth, WA 647	Prospective all ages	1989-90	205	177	191
			1995-6	156	157	157
			2000-1	124	131	128
Oyabe <sup>107</sup>	Rural Japan 2068	Prospective over 25s	1977-81	605	476	
			1982-6	455	322	
			1987-91	417	329	
OCSP <sup>50</sup> & OXVASC <sup>69</sup>	Oxford 429 128 262	Prospective all ages	1981-4	226	228	227
			1986	194	207	201
			2002-4	150	174	162
Rochester <sup>132</sup>	Minnesota 454	Prospective all ages, CI only	1985-9	173	124	147
Framingham <sup>84</sup>	Mass. US 1030	Prospective	1950-77	7.6*	6.2*	
			1978-89	6.2*	5.8*	
			1990-2004	5.3*	5.1*	
GCNKSS <sup>95</sup>	Kentucky 1954	Prospective	1993-4			182
			1999			206
Auckland <sup>51</sup>	NZ 521 1255	Prospective	1981	162	148	135
			1991	113	124	136
Kolkata <sup>100</sup>	India 247	Prospective Questionnaire	2003-5	117.08†	178.01†	145.3†
Matao <sup>133</sup>	Brazil 81	Prospective	2003-4	136†	80†	108† 137†
Sicily <sup>70</sup>	Italy, 62	Prospective	1999-2002	123‡	185‡	154‡
PISCIS <sup>47</sup>	Chile, 292	Prospective	2000-2	103.2	86.5	97.4
Finland <sup>98</sup>	Finland 244 255 594	Stroke register	1971-3	108.3	107.4	107.9 (264.4§)
			1978-80	91.1	95.2	93.2 (181.0§)
			1989-91	201.1	239.6	220.3 (194.7§)
L'Aguila <sup>134</sup>	Italy 4353	Stroke register	1981-91			292 (259‡)
			1994-98			
Dijon <sup>87</sup>	France 3691	Stroke register	1985-89	130.57‡ (88.16†)	73.18‡ (48.47†)	97.87‡ (65.73†)
			1990-94	134.77‡ (88.45†)	80.24‡ (50.78†)	103.22‡ (66.84†)
			1994-99	109.64‡ (72.85†)	68‡ (44.18†)	85.45‡ (56.29†)
			2000-04	124.45‡ (82.82†)	80.09‡ (53.2†)	99.14‡ (66.04†)
FINSTROKE <sup>54</sup>	Finland 5650	Stroke register	1983-97			379 246
Lund-Orup <sup>57,58</sup>	Sweden 456	Stroke register	1983-85	214	199	207 (134‡)
			1993-95	246	225	235 (158‡)
			2001-02	257 (190‡)	203 (104‡)	230 (144‡)
SBSS <sup>117</sup>	Scot, 596	Stroke register	1998-2000			280
STROMA <sup>56</sup>	Sweden 3621	Stroke register age 50-79 only	1989	575appx	320appx	
			1990	657	400	
FINMONICA <sup>135</sup>	Finland 11392	Stroke register 25-74yrs only	1983-85	267	150	
			1990-92	241	129	
Poznan <sup>52</sup>	Poland	Hospital data retrospective	1977			
			1985	216.6 (154.6**)	182.2 (95.8**)	198.3 (121.7**)
Minneapolis <sup>136</sup>	US 3647 4783	Hospital data	1980			416.8§§
			2002			358.7§§
Quebec <sup>88</sup>	Canada 113046	Hospital discharge data	1988	119*** (13†††)	110*** (13†††)	
			1995	120*** (15†††)	119*** (13†††)	
			2002	85*** (15†††)	85*** (14†††)	

**Table 29 - Literature table for studies of stroke incidence**

\* Rates are per 1000 person years

† Standardised to world population

‡ Standardised to European population

§ Standardised to Swedish population

\*\* Age adjusted rates

†† Age adjusted rates

‡‡ Age adjusted rates

§§ Hospitalisation rate only

\*\*\* Infarcts

††† Haemorrhages



Study	Location (n)	Study type	Period	% men	Mean age			↑BP*	IHD	DM	Prev MI	PVD	A Fib	CCF
					Men	Wom	Total							
ARCOS <sup>83</sup>	Auckland, NZ	Prospective <sup>†</sup>	1981-2	49.5	71			47.8	10.9	9				
			1991-2	45	70.6			49.7	15.1	13.7				
			2002-3	46.9	71.8			56	12	15.9				
PCSS <sup>55</sup>	Perth, WA 647	Prospective	1989-90	53.4	76 <sup>‡</sup>			59.4	34.7	12				
			1995-6	49.3	79*			59.2	32.3	15.5				
			2000-1	48.1	77*			56.8	22.4	19.1				
OCSP & OXVASC <sup>69</sup>	Ox., UK 429 128 262	Prospective	1981-4	49	72.3			60.9	15.6	10.5	18.2	11.7	9.6	
			1986	48.4	70.6			56.3	17.2	9.4	10.9	7.8	13.3	
			2002-4	48.1	73.6			45.7	12.2	9.5	12.6	8.8	16.8	
Rochester <sup>60</sup>	Minn., US 454	Prospective	1985-89	41	67-80			72.9	20.7	20.7	11.2		5-33	8.7
Framingham <sup>84</sup>	Mass. US 1030	Prospective	1950-77	48.1	69	69	69	48 (56)	18 (11)	7 (5)			2 (1)	
			1978-89	41.2	73	79		43 (38)	21 (13)	8 (6)			4 (2)	
			1990-2004	41.8	76	81		34 (30)	19 (8)	12 (9)			5 (3)	
GCNKSS <sup>95</sup>	Kentucky, US 1954	Prospective <sup>§</sup>	1993-4	43	63			44	10	14				
			1999	42.3	61			45	10	16				
Sicily <sup>70</sup>	Italy, 62	Prospective	1999-2002	41.9	71.5	74.6	72.5	62	29	26			12	
PISCIS <sup>47</sup>	Chile, 292	Prospective	2000-2	56	61.2	68.5		60		21	9		11	4
Buenos Aires <sup>96</sup>	Argentina 535	Hospital data	2003-6	54.4				77.1	16.3	17			15.5	
Portland <sup>72</sup>	Oregon, US 196	Hospital data	1967-71					24	10	12	13		11	16
STROMA <sup>56</sup>	Malmo, Sweden 3621	Stroke Register	1989	54.4							15.7 (4.2)			
			1990								13 (5.7)			

**Table 30 - Literature table of Stroke studies including comorbidity data – part 1**

\* Figures as total % or male % (female %)

† Not all were first strokes

‡ Median age

§ Comorbidities from the study population, not the stroke subgroup

Study	Location (n)	Study type	Period	% men	Mean age	↑BP	IHD	DM	Prev MI	PVD	A Fib	CCF	CRF	COPD
KCSS <sup>77</sup>	Kansas, US 236	Prospective	2004	44	70		13	23	14			6		14
Dijon <sup>87</sup>	France 3691	Stroke register	1985-89		66 (67.8)	65.3		10.4	22.2	12.1	22.9			
			1990-94		*	61.6		12.6	20.1	9.7	29			
			1994-99			61.9		15.7	25.8	12.9	29			
			2000-04		71 (75.6)	64.1		17.5	17.9	10.2	23.1			
PNSR <sup>71</sup>	Poland 11107	Stroke register	2000		†	72.1	4.6	12.7	6.3		10.7	7.9		
					‡	61.8	42.4	21.2	9.7	23.1	11.9			
					§	64.3	36.6	20.5	12.7	30.8	20			
Barcelona <sup>63</sup>	Spain 1840	Stroke register	1986-1997			53.2	14.5	21.4		7.7	29.6	5.8	2.8	6.8
Barcelona <sup>62</sup>	Spain 1473	Stroke register	1986-1995	52		52	13	20		7.8	27	5.7		5.8
Quebec <sup>88</sup>	Canada 113046	Hospital data	1988		73**	35-38	11-21	11-20		2-4	5-11	3-9	1-5	
			1995			42	10-21	10-23		2-4	6-15	2-8	5-6	
			2002		76 <sup>†</sup>	51-56	22-31	19-27		2-4	18-19	4-8	3-5	
North Carolina <sup>86</sup>	US 843 786	Hospital data	1970-3	46	70 <sup>†</sup>	51	36	17						
			1979-80	48	70 <sup>†</sup>	63	54	29						
GRI <sup>66</sup>	Glasgow, UK 412	Hospital data	2004	49.8	67.9	55.1	35.4	17		4.9		9.2		10.2
VASt <sup>85</sup>	North Carolina, US 1073	Hospital data	1995-7		68.1	58.1	26	36	9.6	5.7	12.7	7.7	1.9	15.3
Portland <sup>72</sup>	Oregon, US 196 247 275	Hospital data	1967-71			24	10	12	13		11	16		
			1974-78			35	14	18	15		16	19		
			1981-1984			56	16	15	14		14	20		

**Table 31 - literature table of stroke studies including comorbidity data - part 2**

\* Male (female) – remainder of studies have age for both sexes combined

† Comorbidity data for haemorrhagic stroke follows

‡ Comorbidity data for ischaemic stroke follows

§ Comorbidity data for unclassified stroke follows

\*\* Median age

Study	Period	CI	ICH	SAH	Other
Rochester <sup>101</sup>	1955-69	79	10	6	5
Rochester <sup>137</sup>	1945-74	75.4	11.3	5.7	7.6
Framingham <sup>102</sup>	1971-81	75	4	10	3
Oxfordshire <sup>50</sup>	1981-86	81	10	5	5
Perth <sup>55</sup>	1989-90	68.9	12.7	4	14.3
	1995-96	77.9	10.3	2.3	9.4
	2000-01	75.4	10.4	6.6	7.7
N Carolina <sup>86</sup>	1970-73	78	14*		8
	1979-80	49	8		43
Copenhagen (MONICA) <sup>109</sup>	1982-91	31.7	8	5.7	54.7
CCHS <sup>124</sup>	1977-92	36.2	6.8	4	53
Finland <sup>98</sup>	1972-73	61	17	17	1
	1978-80	73	11	12	4
	1989-91	79	12	7	2
PISCIS <sup>47</sup>	2000-02	65	23	5	7

**Table 32 - literature table of stroke studies including data on stroke subtype**

Study	Period	30-day Survival					
		Overall	Thrombus	Embolic	ICH	SAH	Other
Auckland <sup>51</sup>	1981-91	67.8					
		75.9					
Oyabe <sup>107</sup>	1977-81	73.2f 82m <sup>†</sup>					
	1982-86	75.5f 85.7m					
	1987-91	80.9f 85.8m					
STROMA <sup>56</sup>	1989-98	90.7f 90m					
PISCIS <sup>47</sup>	2000-02	76.7	82.2		71.1	60	60.9
Kolkata <sup>100</sup>	2003-05	59.92					
GCNKSS <sup>95</sup>	1993-94	86.1	90.6		66	62.8	
	1999	85.3	89.8		62.4	68.7	

**Table 33 - Literature table of stroke studies including 30-day survival data**

\* Data for ICH and SAH presented combined

† Female (f) & male (m) data presented separately

		30-day Survival						1-year Survival					
Study	Period	Overall	Thrombus	Embolic	ICH	SAH	Other	Overall	Thrombus	Embolic	ICH	SAH	Other
Rochester <sup>101</sup>	1955-69	72	81	*	16	48	NA						
Framingham <sup>102</sup>	1971-81	78	85	73	18	54							
Sicily <sup>70</sup>	1999-2002	75.8						60.9					
Oxfordshire <sup>50;138</sup>	1981-86	81	90	*	48	55	26		69	77	38	52	16
Perth <sup>55†</sup>	1989-90	78.1	91.3	*	62.5	60	33.3						
	1995-96	77.5	85.5		54.5	80	35						
	2000-01	79.8	86.2		52.6	75	57.1						
N Carolina <sup>86</sup>	1970-73	86	93	*	32	‡		49	54	*	18	‡	
	1979-80	95	96		70			62	68		55		
Portland <sup>72</sup>	1967-71	67						47					
	1974-78	70						54					
	1981-85	82						64					
Moscow <sup>99</sup>	1972-74	63						48					
Copenhagen (MONICA) <sup>109</sup>	1982-91	72	79		40	56	40	59					
CCHS <sup>124</sup>	1977-92	76.3	91.1		47.6	53.1	75.4	65.2	73.6		42.7	40.8	64.2
Finland EK <sup>98</sup>	1972-73	65.2	77.7		26.8	59.5	61.5	56.6	68.9		19.5	52.4	46.2
	1978-80	70.6	75.5		58.6	54.5	50	60.4	65.4		41.4	54.4	25
	1989-91	76.7	80.6		69.9	46.2	69.2	65.9	68.2		64.4	46.2	53.8

**Table 34 - literature table of stroke studies including 30-day & 1-year survival data**

\* Data for thrombotic & embolic stroke combined

† 28 days rather than 30 days

‡ Data for ICH & SAH is combined