Epidemiology of stroke in an urban population - aspects of time, place and person

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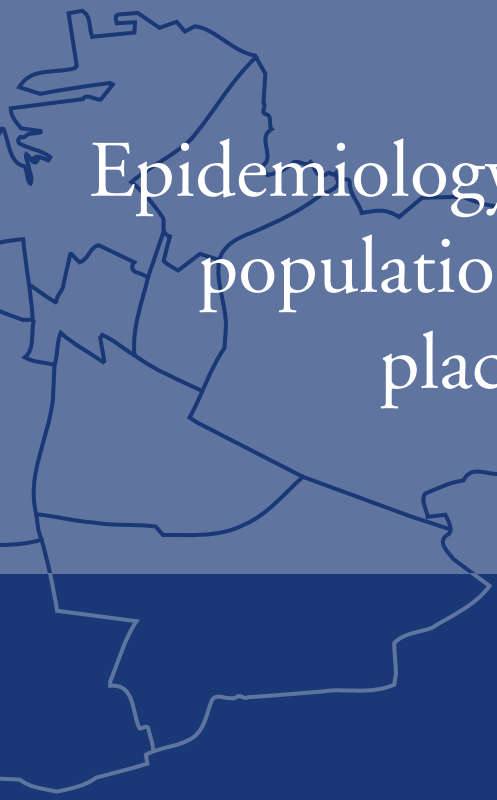

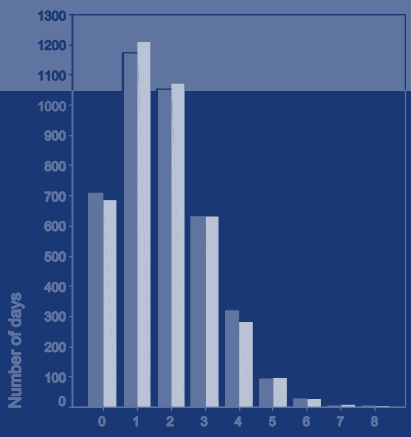

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Abstract

The present thesis explored the epidemiology of stroke in Malmö, Sweden, an urban population of approximately 250000 inhabitants. Incidence of stroke in Malmö has been monitored since 1989. The National census investigation in 1990 was used to get information about the background population in the city.

Previous studies of the seasonal and weekday variations in incidence of stroke have shown inconsistent results. In this study, the temporal variation in stroke incidence was explored among 7129 patients with a first stroke between 1989 and 1999. No relationship could be found between season or weekday and incidence of stroke. However, the mortality rates (within 28 days) were significantly higher among patients with stroke in winter.

Several studies have shown that divorced or widowed men and women have higher mortality rates than those who are married. Whether incidence of stroke similarly differ between these groups is less clear. In a study of stroke incidence in Malmö between 1990 and 2000, we found that incidence of stroke was increased in divorced men and women and in widows/widowers. Never married men had not any increased risk. Among men and women who initially were married, divorce or death of spouse was followed by an increased incidence of stroke.

Previous studies have shown that incidence of stroke varies between countries or between ethnic groups. We explored whether incidence of stroke was related to country of birth. Inhabitants from former Yugoslavia and Hungary had an increased risk of ischaemic stroke. People from former Soviet Union and China or Vietnam had an increased risk of intracerebral haemorrhage, and people born in Finland had an increased risk of subarachnoid haemorrhage. People born in Romania had lower risk than those born in Sweden.

Previous studies from the city have shown that incidence of stroke show substantial differences between the residential areas in the city. Areas with high incidence are characterised by less favorable socioeconomic circumstances. We explored whether the survival among the stroke cases similarly was related to the residential area. The 28-day mortality, 1-year mortality and long-term mortality (until 2001) was higher in patients from areas with low socioeconomic level. These relationships reached significance mainly for the longer follow-up periods and for patients below 75 years of age.

It is concluded that incidence of stroke is related to marital status and country of birth. The residential area and season of the stroke event are associated with the prognosis after the stroke.

Key words: Stroke, case fatality, temporal trends, marital status, life events, stroke outcome, survival, ethnic groups, incidence, epidemiology, geography, Sweden.

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Till min hustru Boel och min dotter Catherine
Till minnet av min far Moksed Ali Khan

“Whoever wished to investigate medicine properly should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces. Then the winds, the hot and the cold, especially such as are common to all countries, and then such as are peculiar to each locality. In the same manner, when one comes into a city to which he is a stranger, he should consider its situation, how it lies as to the winds and the rising of the sun; for its influence is not the same whether it lies to the north or the south, to the rising or to the setting sun. One should consider most attentively the waters which the inhabitants use, whether they be marshy and soft, or hard and running from elevated and rocky situations, and then if saltish and unfit for cooking; and the ground, whether it be naked and deficient in water, or wooded and well watered, and whether it lies in a hollow, confined situation, or is elevated and cold; and the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labor.”

(Hippocrates, "Airs, Waters, Places", 400 BC)

Contents

Abstract

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Key words: Stroke, case fatality, temporal trends, marital status, life events, stroke outcome, survival, ethnic groups, incidence, epidemiology, geography, Sweden.

Definitions

Age standardisation	A procedure for adjusting rates, e.g., death rates, designed to minimize the effects of differences in age composition when comparing rates for different populations.
Case fatality rate	The proportion of cases of a specified condition which are fatal within a specified time. A case fatality rate is calculated as follows: $$\text{Case Fatality Rate (\%)} = \frac{\text{No. of individuals dying during a specified period of time after disease onset or diagnosis}}{\text{No. of individuals with the specified disease}} \times 100$$
Chi-squared test ($\chi 2$ test)	A test to determine whether the proportions or event rates of two or more groups are different.
Confidence Interval	A range of values for a variable of interest, e.g., a rate, constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits. It is the measure of the precision within which one can estimate a mean, proportion or relative risk. In general a confidence interval

	estimate of a given population parameter can be calculated using the following formula: Endpoints of interval=estimate±(confidence coefficient (1.96) X standard error of the estimate), which means that in 95% of cases out of 100 contain the true population value.
Cohort Study	The analytical method of epidemiologic study in which subsets of a defined population (cohort) is followed over a period of time and the effect of exposures (treatment or risk factors) is investigated.
Conditional Logistic Regression	In analysis of data from matched case-control studies, to take into account of matching a method known as conditional logistic regression is used. The logic for conditional logistic regression is the same as McNemer´s test. When the exposure is the same for both case and control, the pair do not contribute to the estimate of the odds ratio. It is only when they differ; one can calculate an odds ratio.
Cox Proportional Hazard	(Proportional Hazard Model) A statistical model in survival analysis developed by D. R. Cox in 1972 asserting that the effect of the study factors on the HAZARD RATE in the study population is multiplicative and does not change over time.

For example, the model for two factors x_1 and x_2 asserts that the rate at time t λ (t), is given by $e^{\beta_1 X_1+\beta_2 X_2}$ λ_0 (t) where λ_0 (t) is the rate when $x_1=x_2=0$, and *e* is the base of the natural logarithm.

Epidemiology

The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems. "Study" includes surveillance, observation, hypothesis testing, analytic research, and experiments. "Distribution" refers to analysis by time, place, and classes of persons affected. "Determinants" are all the physical, biological, social, cultural, and behavioural factors that influence health. "Health-related states and events" include diseases, causes of death, behaviours such use of tobacco, reactions to preventive regimens, and provision, and use of health services. "Specified populations" are those with identifiable characteristics such as precisely defined numbers. "Application to control…" makes explicit the aims of epidemiology- to promote, protect, and restore health.

Incidence Rate

The rate at which new events occur in a population. The numerator is the number of new events that occur in a defined period; the denominator is the population at risk of

	experiencing the event during this period, sometimes expressed as person-time.
Logistic regression analysis	A mathematical modelling approach that can be used to describe the relationship of several independent variable to a dichotomous dependent variable. Given data on a dichotomous dependent variable *y* and one or more independent variables x_1, x_2, *etc.*, regression analysis involves finding the "best" mathematical model to describe *y* as a function of *x´s*, or to predict *y* from the *x´s*.
Mortality Rate (Death Rate)	An estimate of the portion of a population that dies during a specified period. The numerator is the number of persons dying during the period; the denominator is the number in the population, usually estimated as the midyear population.
Nested Case Control Study	A hybrid design in which a case-control study is nested in a cohort study. This design is applied to a population already identified in an existing study, in which cases and controls are drawn from a population which is already under investigation in a cohort study.
Poisson Distribution	Variables that denote the number of occurrences of an event or object in a certain unit of time or space are distributed according to the Poisson distribution named after Simeon Denis Poisson (1781-1840). The distribution is based on the assumption that the events occur randomly,

independently of one another, and with an average rate that does not change over time. It is used to determine the probability distribution of random occurrence of discrete events. The formula for calculating Poisson probabilities is

$$\mathbf{Pr}\,(X = x) = \frac{e^{-\lambda}\lambda^{x}}{x!}$$

Where X represents the variable number of cases in a population, Pr(X=x) represents the probability of observing x cases, e=universal constant and λ represents the average number of occurrences of the event.

Poisson Regression

Poisson regression is a method for multiple regression analysis of cohort data with a dichotomous outcome and one or more categorically defined predictors. It is mostly used in situations when the outcomes of interest are rates (and rate ratio); it is especially suitable for studying rare diseases in large populations. The model specifies that the magnitude of the rate is an exponential function of a linear combination of covariates and unknown parameters.

Relative risk

1. The ratio of the risk of disease or death among the exposed to the risk among the unexposed; this usage is synonymous with RISK RATIO.

2. Alternatively, the ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate in the unexposed, i.e., the rate ratio.

Abbreviations

CI	Confidence interval
CT	Computerized Tomography
FoB	Folk- och bostadsräkning (Population and Housing Census)
HR	Hazards Ratio
ICD code	International Classification of Diseases
IS	Ischemic Stroke or Cerebral infarction (CI)
ICH	Intracerebral haemorrhage
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
OR	Odds ratio
RTB	Register över totalbefolkning, RTB (Population Register)
RR	Relative risk
SAH	Subarachnoid haemorrhage
SCB	Statistiska Centralbyrån (Statistics Sweden)
SES	Socioeconomic status
STROMA	Stroke Register in Malmö
TIA	Transient ischemic attack
WHO	World Health Organization

List of original papers

This thesis is based on the following publications which will be referred to by their Roman numerals:

I. Khan FA, Engström G, Jerntorp I, Pessah-Rasmussen H, Janzon L. Seasonal patterns of incidence and case fatality of Stroke in Malmö, Sweden: The STROMA study. Neuroepidemiology 2005;24:26-31.

II. Engström G, Khan FA, Zia E, Jerntorp I, Pessah-Rasmussen H, Norrving B, Janzon L. Marital dissolution is followed by an increased incidence of stroke. Cerebrovasc Dis 2004;18:318–324.

III. Khan FA, Zia E, Janzon L, Engström G. Incidence of stroke and stroke subtypes in Malmö, Sweden, 1990-2000. Marked differences between groups defined by country of birth. Stroke. 2004 Sep;35(9):2054-8.

IV. Khan FA, Pessah-Rasmussen H, Janzon L, Engström G. Neighbourhood and survival after stroke- an 11-year follow up study of stroke patients in Malmö, Sweden. (Manuscript).

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Introduction

Stroke is a major public health problem in Sweden. The number stroke victims per year in Sweden are around 30,000. It is the third most common cause of death[1]. The total need for inpatient care is higher than for any other somatic disease[2]. The major part of the health care cost in Sweden is related to care and rehabilitation of stroke patients[3, 4].

According to the World Health Organization (WHO) definition, stroke a clinical syndrome characterized by the sudden onset of a focal neurological deficit (or coma) due to infarction of, or haemorrhage into or over, a part of the brain. The deficit persists for longer than 24 hours or leads to earlier death[5]. Episodes that last less than 24 hours are called transient ischemic attacks (TIAs). Figure 1 illustrates a schematic view of pathogenesis of stroke. Stroke is multi-aetiological disease. Cerebral infarction or Ischemic Stroke (IS) that accounts for about 85% of all stroke events in Sweden[6] is mostly caused by extracranial or intracranial large artery atherothromboembolism (50%), small artery microatheroma/ lipohyalinosis (25%), embolism from the heart (20%), blood disease (<5%), non atheromatous arterial disease (e.g. dissection, arteritis) (<5%)[7]. Intracerebral haemorrhage (ICH) accounts for about 10% of all stroke events. The major underlying causes of ICH are hypertensive lipohyalinosis and microaneurysms (40%), amyloid angiopathy (10%) bleeding diatheses (e.g. antithrombotic drugs, thrombocytopenia) (10%), arteriovenous malformation (10%) and aneurysm (8%); less common causes of ICH are arteritis, drugs as amphetamines and cocaine, arterial dissection and intracranial venous thrombosis. Subarachnoid haemorrhage (SAH) accounts for about 5 % of all stroke events, it is caused by bleeding from aneurysm or arteriovenous malformation[8].

As stroke encompasses a heterogeneous group of vascular diseases, many factors predispose to or increase the risk of having stroke. Age is the single

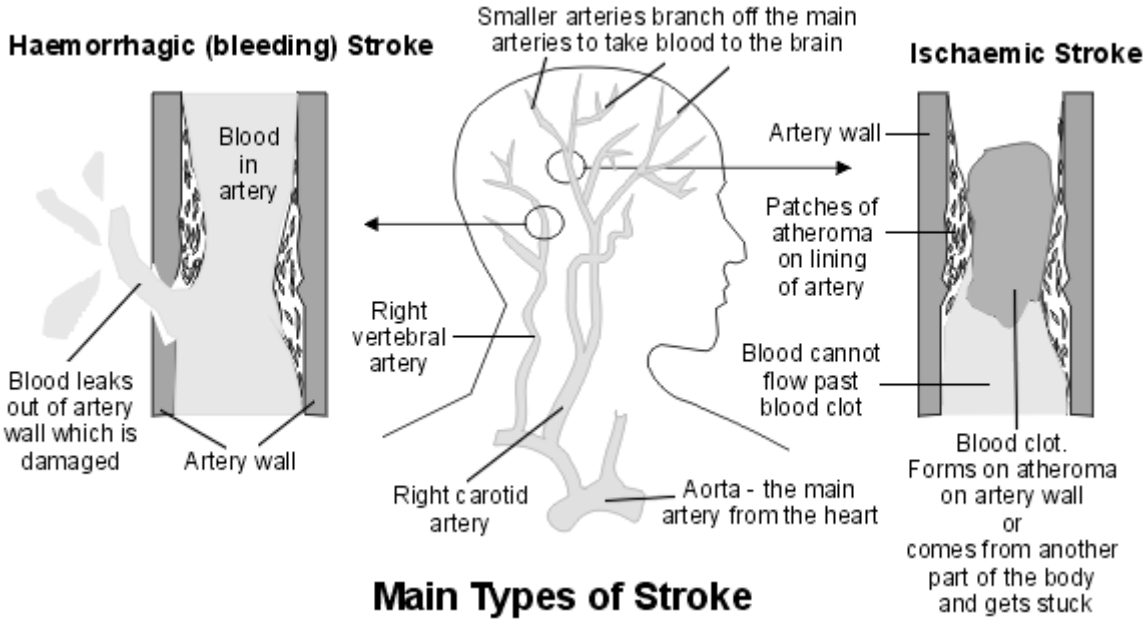

Figure 1. *A schematic view of the brain and type of stroke*

most common factor that predicts a high risk for stroke[9]. The likelihood of stroke is also higher among men[10]. Apart from age and sex other factors that increase the risk of stroke are high blood pressure, smoking, alcohol, family history and previous heart disease and atrial fibrillation[11]. Previous transient ischemic attack (TIA)[12], diabetes mellitus[13], sedentary life-style[14], inferior social circumstances[15], country of residence[16], diet[17], use of particular medications (e.g. oral anti coagulants)[18,19] and climate (cold weather)[20] are reported to be predisposing risk factors. Besides, inflammation can contribute to stroke risk via various interrelated mechanisms[21]. Recently, some studies raised a cautionary flag about the risk of cardiovascular events associated with use of COX-2 inhibitors when used for arthritis and musculoskeletal pain[22]. Infectious diseases, traditional risk factors, and genetic susceptibility may

cooperate in stimulating inflammatory pathways[23]. Stroke is more common among blacks than this among whites[24] and also more common in Eastern Europe than this in Western Europe[25].

The consequence of stroke has been widely studied. The 28-day case fatality rate varied threefold in the WHO MONICA study[26]. Case fatality rates also vary between subtypes of stroke[27]. There is a downward trend in case fatality rate shown in several studies[28.] The risk of recurrent stroke event is highest in the first month and fall gradually over the years. The cumulative rate of death or recurrent stroke over 5 year is about 60%[29]. Recurrent stroke is more common among survivors of haemorrhagic stroke than it is among patients with ischemic stroke[30, 31]. Stroke patients have to live with worsened quality of life even after recovery from most of the functional impairments which cause a huge social burden[32, 33]. Disability, dependency and the social and emotional consequence of stroke and above all quality of life of stroke patients have been widely reported in many studies [34, 35].

Temporal patterns of stroke

The temporal patterns of stroke have been studied in relation to year of incidence, season, weekday and diurnal patterns. In a recent study from Malmö, it was shown that incidence of stroke increased between the time period 1989-1999[36]. This is in accordance with other studies on stroke incidence during the 90´s in Sweden[37, 38], but opposite to the results in a study in Gothenburg studying stroke incidence under the period 1971-87[39]. Seasonal variations of the incidence of stroke have been reported from studies conducted in different parts of the world. The findings are however not consistent. Some have shown an increased incidence in winter[40, 41], while others reported that the highest incidence occur either in autumn [42, 43, 44] or in spring[45]. A recent study from Australia found that the stroke attack rates were

highest in the winter and lowest in the summer. From February (summer) to July (winter), there was a significant increase of the stroke attack rates. This increase was seen mainly in those ≥65 years of age [46]. Case-fatality rates showed similar trends with a 1- to 2-month lag compared with attack rates. Seasonal variations have also been reported for specific subtype of the stroke[47]. Several studies have reported on variability of stroke occurrence by day of the week with higher incidence and case fatality on Monday[48, 49]. Some studies also reported diurnal variation of stroke incidence and fatality rates with peaks in the morning hours[50-52]. To our knowledge, few in the northern Europe have studied case fatality of stroke by season[53, 54].

Marital status, marital dissolution and stroke

Several studies have reported higher mortality rates among unmarried individuals as compared to those who are married[55-63]. Deaths from many different causes, including cardiovascular diseases, contribute to the reduced life expectancy for the unmarried[55, 56, 61]. To what extent marital status is related to incidence and subtypes of stroke is however unclear. Some studies have reported a lower incidence of stroke in married people[64-66]; others reported non-significant differences[59, 67], while in one study risk of stroke was higher in married subjects[68]. Most previous studies in this field have analysed the different unmarried states together[65-68]. In one study incidence of stroke tended to be higher in never married men, widowers and divorced men compared to the married group, although the differences were non-significant[59]. In a study of hospital admissions diagnosed with cerebrovascular disease (ICD 430-438), the proportion of never married and divorced men was higher than expected. However, no consistent relationship between marital status and stroke was observed when men with history of alcoholism were excluded[64].

In recent years, more interest has been shown on the health effects of change in marital status, rather than differences between married and unmarried groups. Longitudinal studies have reported that divorce and widowhood is followed by an increased mortality[55, 56, 62, 69, 70]. No previous study has explored whether incidence rate of stroke is increased during the first years after marital dissolution.

Stroke incidence and migration

Stroke incidences show substantial differences between countries[71]. In the WHO-Monica study, the incidence of stroke was, in general, higher among populations in eastern than in Western Europe. It was also relatively high in the Chinese population studied, particularly among women. The study showed large differences in stroke incidence among populations and case-fatality rates contribute to the more than threefold difference in stroke mortality rates among populations[72]. Widening differences in both attack rates and case fatality rates between East and West were also found[25, 73, 74.] Substantial differences between geographical areas characterised by specific ethnic groups within countries were also noted. A concentration of high stroke mortality rates in the South eastern states in the USA was noted as a persistent distribution pattern which is termed as "the stroke belt" [75, 76]. Studies from the United States, the United Kingdom and other countries [77-89] have shown differences in stroke mortality rates between ethnic groups that only partially can be explained by a higher prevalence of hypertension and other established risk factors[77, 78]. Studies of incidence of stroke are however sparse[77-80], and no previous study have been retrieved in which incidence of stroke and stroke subtypes has been compared among different immigrants groups. Many studies have reported higher stroke mortality rate among immigrants, e.g., among Carribeans in UK[90]. Mortality from cerebrovascular disease was

highest in Caribbeans followed by Africans and Indians who had higher rates than Irish and other west Europeans in UK[82]. However in some studies, lower rates of mortality have been reported among immigrants compared to the indigenous population and to their country of origin. For whites and blacks and for each of the respective race/sex groups in the USA, immigrants had markedly lower age-adjusted stroke mortality rates compared to the entire US-born resident population and the US-born interregional migrant population[91]. Another study in the USA describes that the Native Americans, the Asians and the Hispanics have lower stroke mortality rates than the Non-Hispanic Whites[92]. There are substantial socioeconomic differences between the residential areas in the city of Malmö. Areas with a high incidence of stroke are characterised by inferior socioeconomic circumstances and a large proportion of immigrants[93]. The age-adjusted incidence of stroke has increased in Malmö during the last years[36], and the number of immigrants has increased dramatically. However whether incidence of stroke differs between immigrants from different countries and native born Swedes has been unclear.

Neighbourhood and survival after stroke

Studies on incidence of stroke from different parts of the world showed substantial geographical variations both between and within countries[25, 72, 94]. Studies on stroke incidence and stroke mortality have shown that differences with respect to the prevalence of cardiovascular risk factors, as well as the socioeconomic circumstances, could account for a major part of these differences[93, 95]. The geographical differences in disease occurrence could hence indicate a potential for prevention. However, whether short- and long-term survival after stroke similarly is related to the geographic area is less clear. Studies on long-term survival after stroke are particularly uncommon in this context.

The city of Malmö, is divided into 18 administrative areas. Previous studies have shown that the incidence of myocardial infarction and of the short and long-term rates of survival after MI differ between the areas[96, 97]. A recent study from the Stroke Register of Malmö, Sweden (STROMA), showed that the incidence of stroke in these areas ranged from 437 to 743 for men and from 223 to 518 among women, and that incidence of stroke was significantly associated with the socioeconomic level of the area[93]. Whether the short and long-term survival after stroke differs similarly between the areas has been unclear.

Aims

General aim

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations. Distribution refers to analysis by time, place and classes of person's affected[98]. The general aim of this thesis was to study the different aspects of stroke epidemiology, by exploring the relationships with season and week-days (time), residential area (place) and ethnicity, marital status and marital dissolution (person).

Specific aims

- To investigate the weekly, monthly and seasonal variations in incidence and 28-day case-fatality of stroke (Paper I).
- To investigate the marital status-specific incidence of stroke, and the risk of stroke following marital dissolution, in an unselected urban population (Paper II).
- To investigate the incidence of stroke and stroke subtypes in relation to country of birth (Paper III).
- To investigate whether short- and long-term survival after first-ever stroke was related to the socioeconomic circumstances of the residential areas (Paper IV).

Study population and design

STROMA

A stroke register to collect data on all stroke cases in Malmö (STROMA) was established in 1989[99]. The purpose of the register was to monitor incidence of stroke in the population of Malmö from Jan 1st, 1989, and onwards. Both in-patients and out-patients are included. STROMA consists of two parts, an incidence register and a recurrence register. The incidence register includes all patients who had their first stroke after January 1989. Recurrent stroke after 1989 are also included. The recurrence register includes recurrent stroke events among patients who had the first stroke event before 1989. Only the incidence register has been used in this thesis and only the first ever stroke event have been studied.

The criterion of stroke was according to World Health Organization definition of stroke, which is rapid development of clinical signs of local or global loss of cerebral function lasting for more than 24 hours or leading to death within 24 hours, with no apparent non-vascular cause[5]. By definition patients with transient ischemic attacks were excluded. With the use of International Classification of Disease, Ninth Revision (ICD-9), cases were classified as subarachnoid haemorrhage (SAH, ICD-9 code 430), intracerebral haemorrhage (ICH, ICD-9 code 431), cerebral infarction (CI) or Ischemic Stroke (IS) (ICD-9 code 434) and undetermined pathological type of strokes (UND, ICD-9 code 436)[100]. The diagnosis of stroke was preliminarily established based on history and symptoms. Clinical investigations were mainly used for subtype classification. The diagnosis ICH (431) was confirmed by CT and/or autopsy; the diagnosis CI (434) was established when

CT and or/autopsy confirmed CI or excluded ICH and non vascular causes; if neither CT, nor autopsy were undertaken, the stroke was classified as UND (436). SAH (430) was confirmed by CT, lumbar puncture or autopsy.

Quality of STROMA

The accuracy of the diagnosis in STROMA has been ensured by critical appraisal of each case by a specialized research nurse under the supervision of a senior physician. The case-finding is conducted by a "hot-pursuit" approach. Patients hospitalised due to stroke are "pursuited" at the emergency unit and at the in-patients wards of neurology and internal medicine. Non-hospitalised patients referred from the primary care as well as patients who suffer a stroke while hospitalised for other diagnosis (e.g. myocardial infarction, hip fracture) are "pursuited" at the neurology out-patient clinic. The case-finding of the STROMA register includes a broad search among patients with neurological symptoms (loss of motor function, vertigo, loss of vision, headache, etc.) which could indicate a stroke event. The medical records of these patients are searched for previous stroke events and the present and previous episodes are validated according to the stroke criteria. For each stroke event that fulfils the stroke criteria, approximately 10 medical records have been scrutinized.

The STROMA register takes advantage of the infrastructure of the health care in Malmö. There is only one hospital for a background population of approximately 250,000 individuals during the study period. Patients with acute stroke symptoms mostly go directly to the emergency unit, and no referral note is needed. If they contact the primary care first, they are directly sent to the hospital in case of acute symptoms or referred to the neurology out-patient clinic if the patient shows any history of stroke symptoms. Nursing homes cooperate with the hospital and in case of stroke event at the nursing

home patients are directly sent to the hospital. Until 1995, all nursing homes were contacted regularly in order to ensure that all cases had been covered by STROMA. However, it was found that all cases were refereed to CT examinations, and retrieved by the case-finding procedure at the hospital. The nursing homes were therefore not systematically visited after 1995.

One question is whether some patients were missed who died from stroke outside hospital. This was addressed in a study by Dr. Helene Pessah-Rasmussen (unpublished). The autopsy records of all out-of-hospital deaths during the years 1989-1990 were reviewed. During this period, autopsy examinations were performed for virtually all out-of-hospital deaths in the city. During these two years, seven stroke cases that died out-of-hospital were missed by STROMA. This was approximately 0.6% of all stroke events during these two years. This is in accordance with the observations from an ongoing quality assurance, in which individuals who died from stroke according to the cause of death register, and who were not included in STROMA, have been reviewed. These investigations have shown that very few cases that fulfil the stroke criteria can be added by using the cause of death register. On the contrary, stroke cases that are included in the cause of death register and not in STROMA are almost exclusively false positive cases.

Many patients with stroke (approximately 25%) will later have a recurrent event[101]. The recurrence rate of stroke among STROMA incidence cases was almost close to those figures. One measure of the completeness of the register could be the number of stroke events that are detected, and that should have been detected previously. This number is very small (less than 6 per year) and mainly citizens from Malmö that suffered from stroke abroad or at another hospital in Sweden. During the period from October 1st, 2004, to February 28th, 2005), only 1 case was detected that should have been detected earlier. This patient suffered from stroke in 1999 and was treated at a hospital in the

north of Sweden. During this period, approximately 300 stroke events were included in STROMA and about 3000 medical records were searched.

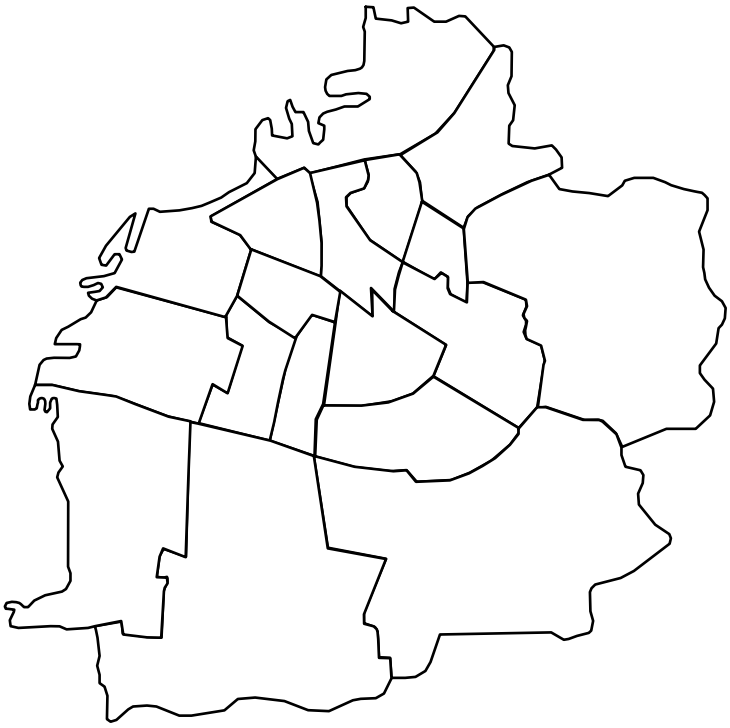

Figure 2. *Map of the city of Malmö and it´s geographical areas*

Record linkage with other national registers

The STROMA register has been linked with other national register. The Population Census Data[102] from 1990 includes information about all (232000) inhabitants in Malmö (Fig. 1) residing in 18 areas. The population living in the city on 1st November, 1990 has been followed up by record linkage with other data bases until 31st January 2001 or until death, or emigration from Malmö. Information about income and socioeconomic status during this period was retrieved from the Total Population Register[103]. Information about cause of death was collected from The National Register of Cause of Death [1].

Residential areas and socioeconomic score

Malmö's citizens live in 18 areas that exhibit substantial differences in terms of socioeconomic circumstances and number of inhabitants[104]. The harbour area was excluded from the study because so few people lived there; thus, a total of 17 areas were studied. Socioeconomic profile of the areas is based on official statistics from the Malmö City Council and data from Statistics Sweden. We have created a socioeconomic score for each area calculated from the following indicators per area: migration rate, percentage of residents with foreign citizenship as a proportion of all citizens with foreign background, dependency of social welfare support (with negative signs), and employment rate (with positive sign). Migration rate was defined as the proportion of all inhabitants who during 1991 moved to another area or left Malmö. As a measure of social integration of the immigrants in the areas, we have calculated the percentage of residents with a foreign citizenship of all inhabitants with foreign background in a specific area. Foreign background was defined as foreign citizens, Swedish citizens who were born foreign citizens or children under 18 years of age with one or both parents foreign born. Dependency of social welfare support was defined as the percentage of all individuals in each area that received social welfare support in 1991. Employment rate was defined as the percentage of all inhabitants between 20 and 64 years who in 1990 had work in the free labour market. The variables were standardized by subtraction with the mean level for all areas in Malmö and divided by the standard deviation for all areas before they were totalled to a score[105]. These 4 parameters were selected to reflect different aspects of socioeconomic deprivation in Sweden today. The socioeconomic score correlates with other well-known measures of social status; e.g., mean income and unemployment rate[94]. The socioeconomic score has in several previous

studies been associated with pattern of disease[98]. The 17 areas are thus categorized into high, medium and low areas.

Statistical methods

Paper I

Month, season and the day of the week were calculated from the date of stroke. Seasons were divided into spring (March, April, and May), summer (June, July and August), autumn (September, October and November) and winter (December, January and February). Case fatality rate was defined as death within 28 days after the onset of the symptom and this was ascertained by verifying with The National Register of Cause of Death [1]. Case fatality rate was studied in relation to day of stroke onset. Age-specific incidence and case fatality rates were calculated in 5 age groups (<=54, 55-64, 65-74, 75-84 and 85- years). The age-specific incidence rates were determined by dividing the average annual number of new cases over the 11-year period by the average number of population of the relevant age group in Malmö during this period. Assuming that the size of the monitored population in Malmö does not vary by season,. $\chi 2$ test was performed to test the seasonal differences. To evaluate whether the incidence and fatality of stroke occurred randomly in a span of 4017 days (January 1989 to December 1999), a Poisson model's goodness of fit test was conducted[106]. Poisson regression analysis[107] was used to calculate the case fatality rate ratios and corresponding 95% confidence intervals (CI) adjusting for sex and age at the onset of stroke to estimate the effect of time on fatal outcome of stroke.

Paper II

Cox proportional hazards model[108] was used to compare incidence rates in categories of married and unmarried individuals, with adjustments for potential confounders. Individuals who changed marital status during follow-up or moved out from the city were censored at the date of change. Pearson chi-square and conditional logistic regression[109] was used to compare the proportion with marital dissolution in cases and controls.

Paper III

The expected number of stroke cases in the immigrants groups was calculated by standardisation for age (5-year bands) and sex using the indirect method. Cox proportional hazards model was used to compare incidence rates with adjustments for age, sex, marital status and socioeconomic indicators.

Paper IV

The association between different areas in Malmö and survival after stroke was analysed using Cox proportional hazards regression model with adjustments for potential confounders. The proportional hazards assumption was evaluated for all variables by comparing estimated log-log survivor curves for the different variables. Tests for trend were performed by introducing neighbourhood groups as an ordinal variable in regression.

All the statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software package[110] and STATA Statistical Software package[111]. P values of <0.05 were considered statistically significant.

Ethical clearance to conduct this research project was obtained from the Ethics Committee of Lund University.

Results and conclusions

Paper I:

Seasonal Patterns of Incidence and Case Fatality of Stroke

The temporal patterns of incidence and case-fatality of stroke was studied among all patients with a first ever stroke between 1989 and 1999 (7,129 patients, 3,313 men and 3,816 women). The mean age was 75.1 years. The incidences occurred during these 4,017 days of observation with a mean of 1.77 strokes per day ranging from no cases to 8 cases per day. The log-likelihood ratio of the goodness of fit statistics was not significant, suggesting that the stroke cases were not grouped within a certain cluster of days during the observation period of 4,017 days.

Season

Incidence of all stroke types together, ICH and SAH showed no variation by season. Incidence of cerebral infarction for both sexes was however higher in autumn and winter. For 28-days case fatality rate, winter emerged as the peak season among men (12.5%), women (17.2%) and total population (15.1%). The relationship between 28-day case fatality and season was significant even after adjustment for age in women ($p<0.05$) with a trough in summer and peak in winter (RR 1.4, 95% CI 1.1–1.8), but among men the pattern was not significant.

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Month

The incidence of stroke did not show any significant monthly variation. For total cases, case fatality rate was highest in February (17.6%) and lowest in September (10.0%). Among women, the age-adjusted case fatality rate ratio was significantly higher in January (RR 1.9, 95% CI 1.2-3.0), February (RR 2.1, 95% CI 1.4-3.3), March (RR 2.0, 95% CI 1.3-3.3) and May (RR 1.7, 95% CI 1.0-2.6) as compared to August. The age-adjusted case-fatality ratios between months were not significant in men.

Weekday

Although not significant, the most frequent day for stroke incidence was Wednesday for men and total population. Tuesday emerged as the peak day for women. The lowest incidence of stroke occurred on Saturday for men and Sunday for women and total population. The age-adjusted rate ratios for fatal cases on weekdays was neither significant in the total population nor in men and women. There were neither any differences of incidence of stroke subtypes across the weekdays.

Conclusions

Case fatality rate following stroke demonstrates a seasonal variation with a peak in winter. Incidence of stroke showed no consistent association with season, month or weekdays.

Paper II:

Marital status, marital dissolution and stroke

Incidence of stroke in relation to marital status

All citizens of Malmö aged 40-89 in 1990 were followed until the last day of December 2000. Those who died, moved out from Malmö or changed marital status were censored on the day of change. A total of 2822 men and 3362 women had a first-ever stroke during the follow-up period. Of them, 2594 men and 3047 women had not changed marital status before the stroke event. Divorced men and women had significantly higher incidences of stroke. This relationship remained significant after adjustment for age, income, country of birth and self-owned home (Figure 2).

High rates of stroke were also observed for widows/widowers. After adjustments, this relation was significant for women only. Incidence of stroke was not significantly increased in never married men or women. The adjusted relative risks for divorced and widowed individuals were higher in young men and women as compared to the older age group. In never married women below 65 years of age, a significantly increased risk of stroke was observed.
Approximately 5% of the men and 4% of the women cohabited with a partner without being married. The results were virtually unchanged if cohabiting men and women were classified as married.

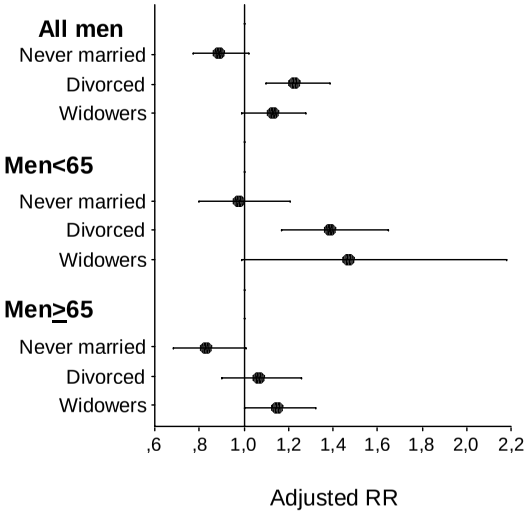

Figure 3. *Incidence of stroke by marital status in all men and in men above and below 65 years of age. Relative risks (95%CI) adjusted for age, income, self-owned home, country of birth (reference: married men).*

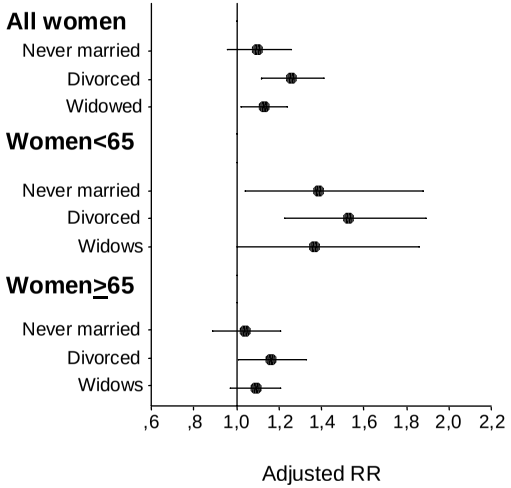

Figure 4. *Incidence of stroke by marital status in all women and in women above and below 65 years of age. Relative risks (95%CI) adjusted for age, income, self-owned home, country of birth (reference: married women).*

Stroke subtypes

The increased stroke rates in divorced men were consistent for ischemic and haemorrhagic stroke. For divorced women, this was mainly explained by an increased incidence of ischemic stroke.

Incidence of stroke following marital dissolution

Initially married subjects with stroke were compared with initially married controls, matched for age, sex, and vital status at the time of the stroke event. In men and in young women, there was a higher proportion that had been divorced or widowed before the date of stroke among stroke cases as compared to matched controls. No relationship was observed in older women.

The relationship between risk of stroke and time from marital dissolution appeared to be highest 1-2 years after the divorce or death of spouse in men.

Conclusions

The incidence of stroke is higher in divorced and widowed individuals. Never married men have not any increased incidence. The risk of stroke is elevated during the first years after divorce or death of spouse.

Paper III:

Stroke incidence among immigrants

Incidence of stroke among immigrants from specific countries

All inhabitants aged 40-89 years in 1990 were followed until stroke, death, emigration or December 2000. The stroke risk showed substantial differences between immigrants from different East European countries. Immigrants from former Yugoslavia and Hungary showed significantly higher incidences. Although not significantly, immigrants from the former Soviet Union also had higher risk. In contrast, no increased risk was observed among immigrants from former Czechoslovakia or in the large group of immigrants from Poland. Rumanian immigrants had a significantly lower risk. The immigrants from Denmark, Norway, Germany, Chile and Finland had approximately the same risk as citizens born in Sweden. The higher risk in Yugoslavian and Hungarian immigrants and the reduced risk in Rumanian immigrants were consistent in men and women. The higher risk in immigrants from China/Vietnam was mainly observed in women.

Subtypes of stroke

There was a large proportion with intracerebral haemorrhage (ICD-9 code 431) among immigrants from the People's Republic of China and Vietnam. Of the 18 stroke cases in this group, 5 had an intracerebral haemorrhage. The increased risk of intracerebral haemorrhage in this group was statistically significant (RR=4.2, CI: 1.7-10.4) after adjustments for age, sex, marital status, income and self-owned home.

After adjustments for potential confounders, an increased risk of intracerebral haemorrhage was also observed in immigrants from the former Soviet Union (RR=2.7, CI: 1.01-7.3).

Table 1. Incidence of stroke over 10 years of follow-up in relation to country of birth in 118134 citizens, 40-89 years old, in Malmö, Sweden.

Country of birth	Follow-up (person-years)	No of stroke		SAH/ICH/CI/UND* (%)	Relative risk† (95% CI)	Relative risk‡ (95% CI)
		Observed	Expected			
Sweden	813574	5478	5478	2/10/76/12	1.00	1.00
Germany	12786	78	76.0	3/13/67/18	1.01 (0.81-1.3)	1.00 (0.80-1.2)
Former Yugoslavia	31061	132	92.3	2/12/83/2	1.43 (1.2-1.7)	1.31 (1.10-1.6)
Chile	2819	7	7.6	0/14/57/29	0.89 (0.43-1.9)	0.79 (0.38-1.7)
Denmark	21571	116	124.5	2/10/84/4	0.96 (0.79-1.1)	0.91 (0.76-1.1)
Poland	19675	87	83.4	1/9/77/13	1.03 (0.83-1.3)	0.96 (0.78-1.2)
Finland	11751	49	44.0	10/4/78/8	1.12 (0.84-1.5)	1.07 (0.81-1.4)
Norway	3966	21	24.3	0/5/95/0	0.88 (0.57-1.4)	0.87 (0.56-1.3)
Rumania	3515	2	13.6	50/50/0/0	0.14 (0.04-0.58)	0.13 (0.03-0.52)
Former Soviet Union	2409	22	14.9	5/18/68/9	1.49 (0.98-2.3)	1.41 (0.92-2.1)
Czechoslovakia	3969	16	16.1	0/6/94/0	0.99 (0.61-1.6)	0.95 (0.58-1.5)
Hungary	9801	56	41.2	2/12/82/4	1.40 (1.07-1.8)	1.33 (1.02-1.7)
China/Vietnam	2374	18	10.8	6/28/67/0	1.69 (1.07-2.7)	1.50 (0.94-2.4)

*SAH subarachnoid haemorrhage, ICH intracerebral haemorrhage, CI cerebral infarction, UND undetermined subtype
†Relative risk adjusted for age and sex
‡Relative risk adjusted for age, sex, marital status, annual income and self-owned home.

Immigrants from Finland had a significantly higher incidence of subarachnoid haemorrhage (RR=2.8, CI: 1.1-6.8). Of the 49 stroke in this group, 5 were subarachnoid haemorrhages.

Ischemic stroke (ICD-9 codes 434 or 436) were significantly more common in the groups from former Yugoslavia and Hungary (RR=1.34, CI: 1.11-1.62 and RR=1.33, CI: 1.01-1.77, respectively, adjusted for confounders).

Additional analyses

In an additional analysis, the subjects were followed until death, first stroke event, migration from the city of Malmö, or to the beginning of the first year they were without income according to the assessment of taxes. The results, for all stroke cases and for stroke subtypes, were essentially unchanged when subjects without income were censored (not shown).

Conclusions

In this urban population from Sweden, there are substantial differences in stroke incidence and stroke subtypes between immigrants from different countries. To what extent this could be accounted for by exposure to biological risk factors remain to be explored.

Paper IV:

Neighbourhood and survival after stroke

The relationships between neighbourhood and survival after stroke was studied among all patients with first-ever stroke during 1989-2000. The patient cohort consisted of 7680 stroke cases, 54% of whom were women. The mean age was 72 years (standard deviation=11.7, range=94 years) for men and 77.7 years (standard deviation=11.3, range=93 years) for women.

The mean follow up time was 3.5 years. In table 2, the number of patients with first ever-stroke and the proportion of survivors are shown by age group and residential area. Both male and female patients living in the areas having high socioeconomic score had higher 28-days and long-term survival rates than had those living in a neighbourhood with lower socio-economic score. These differences increased with increasing time of follow-up.

Cox proportional hazards regression analysis confirmed that the 28-day, 1-year and long-term survival rates were higher in residential areas with high socioeconomic level independent of age, year of stroke and stroke subtype (Table 3). The differences in 28-day survival did not reach significance. The 1-year survival rates for all men and for women <75 years of age showed significant geographical differences. The long-term risk of dying is higher both among men and women living in a disadvantageous neighbourhood.

Table 2. Proportion of patients surviving 28 days, 1 year and the whole study period after first ever stroke by neighbourhood residence among men and women.

		Men				Women			
		N (%)	28 days survival (%)	1 year survival (%)	Long-term survival (%)	N (%)	28 days survival (%)	1 year survival (%)	Long-term survival (%)
Age <75 years									
Neighbourhood residence	High	391 (21.0)	93.6	87.5	65.7	226 (18.1)	95.1	90.3	69.9
	Medium	719 (38.7)	91.2	84.0	59.1	555 (44.4)	92.4	86.3	63.6
	Low	750 (40.3)	92.5	84.9	57.1	468 (37.5)	90.8	83.1	59.8
	Total	1881	92.3	85.1	59.7	1259	92.3	85.8	63.3
Age >=75 years									
Neighbourhood residence	High	281 (16.8)	87.5	71.2	28.8	388 (13.4)	84.8	64.9	32.5
	Medium	766 (45.7)	84.1	65.0	27.4	1342 (46.4)	81.4	63.5	28.6
	Low	630 (37.6)	84.0	63.0	22.5	1164 (40.2)	82.0	63.2	25.1
	Total	1691	84.6	65.3	25.8	2930	82.1	63.6	27.7
Total population									
Neighbourhood residence	High	672 (18.8)	91.1	80.7	50.3	614 (14.7)	88.6	74.3	46.3
	Medium	1485 (41.6)	87.5	74.2	42.8	1897 (45.3)	84.7	70.2	38.9
	Low	1380 (38.6)	88.6	74.9	41.3	1632 (39.0)	84.5	68.9	35.0
	Total	3572	88.6	75.7	43.6	4189	85.2	70.3	38.5

Causes of death

Among men who died within 1 year, the underlying cause of death were cardiovascular disease (CVD) among 80.1% (stroke among 55.2% and coronary heart disease (CHD) among 16.6%), 8.2% from cancer and the rest from other causes. Among women the corresponding proportions were 86.2% for CVD (60.9% from Stroke, 13.5% from CHD), 4.4% from cancer and the rest from other causes.

Conclusions

Long-term fatality rate after stroke is higher among patients from residential areas with inferior socioeconomic circumstances. The reasons for this relationship remain to be explored.

Table 3. Hazard ratios (95% CI) for stroke fatality according to neighbourhood.

	28 days RR (95% CI)	**1 year RR (95% CI)**	**Long-term RR (95% CI)**
Men			
High	1	1	1
Medium	1.31 (0.98-1.75)	1.25 (1.02-1.52)*	1.05 (0.93-1.19)
Low	1.26 (0.93-1.69)	1.30 (1.06-1.56)*	1.18 (1.04-1.34)*
P for trend**	0.241	0.02	0.005
P for trend ***	0.325	0.034	0.009
Women			
High	1	1	1
Medium	1.33 (1.02-1.72) *	1.15 (0.96-1.37)	1.14 (1.01-1.28)*
Low	1.31 (1.01-1.71)*	1.16 (0.97-1.39)	1.16 (1.03-1.32)*
P for trend**	0.120	0.173	0.032
P for trend ***	0.233	0.315	0.077

* P<0.05, ** Adjusted for age, *** Adjusted for age, year of incidence and stroke sub-type.

General discussion

The purpose of the present thesis was to study different aspects of stroke epidemiology, by exploring the incidence of and/or prognosis after stroke in relation to season and weekday, marital status, ethnicity and residential area. There were no significant seasonal or weekday variations in incidence of stroke. Incidence of stroke was related to marital status, and marital dissolution. Several immigrant groups had an increased risk of stroke. The fatality rates after the stroke events were increased among patients who suffered a stroke in the winter and among patients from areas with low socioeconomic circumstances.

Risk of stroke related to civil status

The present study found a higher incidence of stroke among divorced and widowed individuals. Psychosocial factors like social support, social network and above all social capital are important predictor for healthy lifestyle[112]. Marital dissolution or living alone can have negative impact on all these psychosocial factors. Higher risk of mortality from stroke was identified among socially isolated persons in several studies[113, 114]. A number of additional studies identified higher case fatality after stroke[115], poor recovery in terms of physical and mental wellbeing[116,117] or poor quality of life[118], suicidal thoughts[119] and post-stroke depression[120] among stroke patients with low social capital. The social support offered by marriage could be protective, health behaviour could differ between married and unmarried people, and healthy individuals could be selected into marriage more often than unhealthy. It also has been suggested that the protective effects of marriage are stronger for men than for women[58].

The present results show that the increased risk of stroke in divorced and widowed individuals is largely similar for men and women. The finding of similar or lower risks in never married men suggests that selection of healthy individuals into marriage has little importance for the relationship between marital status and stroke.

Although stressful life-events often are considered to be potential triggers of stroke, not much is known about the stroke risk following a life-event[121]. In a recent study of parents who lost their children, no increased risk of suffering from stroke could be found[122]. In men and in women of younger age-group, we found that marital dissolution before the date of stroke was significantly more common in stroke cases as compared to matched controls. Psychological distress has previously been associated with an increased incidence of stroke[64, 123-125] and there is some evidence for an association with development of hypertension[126]. However, even though the results could be explained by increased psychological stress after marital bereavement, there are other possible explanations. For example, an unhealthy life-style could cause marital dissolution. Divorce or death of spouse could also lead to increased smoking, alcohol consumption and reduced personal care.

Incidence of stroke and country of birth

The present study showed marked differences in stroke incidence and stroke subtypes by country of birth. Incidences of all stroke and ischemic stroke were significantly higher among immigrants from Hungary and former Yugoslavia and incidence of intracerebral haemorrhage was increased among immigrants from the Soviet Union and China or Vietnam. The Finnish group had a significantly higher incidence of subarachnoid haemorrhage. Immigrants from Rumania had a significantly

lower stroke incidence. These differences remained significant after adjustments for age, sex, marital status and socio-economic indicators.

According to official statistics, there are substantial differences in stroke mortality between countries and regions [127]. Studies on stroke incidence have often showed smaller differences between countries as compared to the stroke mortality[16]. Although the comparability of stroke mortality statistics often has been questioned, East European countries generally have high rates of stroke mortality[127,128]. A high incidence of intracerebral haemorrhage has been reported in East Asia[129] and multinational comparisons of subarachnoid haemorrhage have shown high incidences in Finland[130]. With exception of the lower incidence among Rumanian immigrants, our findings are in accordance with those observations. These suggest that the increased incidences among these immigrant groups reflect influences from their original countries.

There were however great differences between immigrants from different countries in Eastern Europe. No increased incidence was observed in Czechoslovakian immigrants or in the large Polish group. Even though the stroke mortality in Eastern Europe generally is much higher than in Sweden[20, 21], it also has been reported that the stroke incidence in Poland is similar to countries from western Europe[131]. The differences between the immigrant groups could partially reflect the circumstances in the original countries. However, another possible explanation is that the circumstances and reasons for moving to Sweden have been different. For example, Yugoslavian immigrants that arrived during the sixties and seventies were often recruited as workers, while Czechoslovakian and Polish immigrants that arrived during the 80s often were higher educated. Incidence of stroke was also comparatively low in

the Chilean group. This suggests that immigrants from these countries are selected groups of more healthy individuals.

Quite unexpectedly, Rumanian immigrants had a significantly lower risk. Only 2 stroke incidences occurred during 3500 person-years as compared to the expected number of 14 and both were hemorrhagic. Studies of immigrant groups e.g. all cause mortality in Turkish people living in Germany[132] or stroke mortality in immigrants to the US[86] have sometimes shown paradoxically lower mortality rates among immigrants as compared to the native born population and the population in the original country. The reasons for the lower mortality rates are controversial and several explanations have been proposed, e.g., highly selected groups of immigrants and the difference in the speed by which risk factors and protective factors change after migration [86,132]. It has also been suggested that this could be explained by foreign-born people that re-migrate without reporting this to the authorities, which could exaggerate the population at risk and cause too low risk estimates for the immigrants[133]. A study from the Statistics Sweden estimated that approximately 25-50,000 foreign-born individuals that officially live in Sweden have left the country[135.] However the results were essentially the same when individuals who were without income were censored. We therefore believe that re-migration was a minor problem in this study. It remains to be explored whether the low incidence in the Rumanian group could be explained by a highly selected group that emigrated from this country, or whether there are other explanations for that. We have studied all the large migrant groups living in this city in 1990. Since then new groups from the Middle East and the former Yugoslavia have migrated which remains to be further studied.

Temporal variations of incidence and case fatality rate

Previous studies have reported a seasonal variation in CI. In this study, a seasonal difference in CI was found for both sexes together. However, this was no longer significant when UND and CI was combined. Temporal variations in the use of CT could bias the results for different stroke sub-types especially in case of UND and CI. It is also possible that the detection rate for CI is higher in the winter because patients are more likely to be admitted with other diseases then. However, as the seasonal variation was non-significant when CI and UND was combined, it is our conclusions that no clear relationship between stroke incidence and season could be found.

In our study we found evidences of seasonal pattern of case fatality. These differences were significant for all strokes and strokes of subtype SAH and ICH among women but did not reach significance for men. The studies conducted on temporal variations in case fatality in Nordic countries is very scarce. However in accordance with the present results, one study in Finland found that the 28-day case fatality rate of CI was significantly different in women with lowest rate in summer[53]. Case fatality rate reflects the severity of stroke as well as the quality of care of the patients. As the hospital staffs have longer vacation periods during the summer than any other season and some ward units close some functions etc, there is no reason to believe that improved care during the summer explains the lower case fatality.

Some biological reasons must be taken into consideration to seek the possible explanation of seasonal variation in case fatality. The increased case fatality in winter could be secondary to other illness. Unpublished data from the city of Malmö show that mortality from all causes show a similar seasonal variation (Khan FA). The seasonal variation in influenza

infections is well known. High blood pressure is an established risk factor for onset, prognosis and survival after stroke[135] and it is known that exposure to cold causes peripheral vasoconstriction and increase in blood pressure [136, 137]. These factors might explain the increased case-fatality in winter or early spring. There is evidence that fibrinogen is a significant predictor of stroke[138,139]. Some studies showed that plasma fibrinogen concentration and blood viscosity varied significantly in different seasons [140,141]. Seasonal variations in other factors such as diet and exposure to sunlight can play a role and variations in temperature are considered as the main reason for the variations of those factors[142]. Other studies in Australia[46] and Finland[53] further strengthen the conclusion that the observed difference in case fatality was not just due to chance.

We found a few reports conducted about the relation of the day of the week and occurrence, and fatality of stroke. Although not significantly, we found that the weekend (Saturday or Sunday) had the lowest incidence but the highest case fatality rate. This was true both for men and partially for women (lowest incidence on Sunday). In a study conducted in Australia, no significant variation of stroke occurrence in weekdays in the community-based population was found; however among hospital-based cases Wednesday had the highest frequency and weekends had the lowest frequency similar to our study[143]. In the Framingham study Monday emerged as the most frequent day for stroke[49].

Neighbourhood and survival after stroke

Incidence of stroke shows substantial differences between the residential areas in the city of Malmö, with higher incidences in areas with inferior socioeconomic circumstances. This study explored whether survival after a first stroke events also was related to the socioeconomic level of the areas.

After adjustment for age, year of stroke and stroke subtype, high socioeconomic level was associated with higher long-term survival rates among all men and women below 75 years. Although not statistically significant, 28 –day survival also tended to be better in areas with high socioeconomic level. The results are in accordance with previous studies from the city, showing geographical differences in incidence of stroke[93, 144], myocardial infarction[145] and survival after myocardial infarction[96, 97]. Together these results suggest that individuals with low socioeconomic circumstances should be a target group for intensified primary and secondary prevention. Further studies need to be conducted to formulate preventive measures.

The reason for geographical difference remained to be explored. It has previously been shown that the prevalence of risk factors in the general population, e.g., hypertension and smoking, is higher in areas with inferior socioeconomic circumstances[71, 146, 147].Whether the areas also are associated with more risk factors among the patients is unknown. This could hypothetically cause stroke events of a higher severity and increase risk of mortality after the events.

It is also possible that secondary prevention, and compliance with the preventive measures, could be different. Treatment of hypertension has been associated with socioeconomic circumstances in some studies, but the results have been inconsistent[148]. The primary care in this city is well organized with universal access and is provided at a low cost in all areas. Previous studies show that, if anything, treatment of hypertension seems to be more common in low SES areas. However, we do not know whether compliance with the treatment differs between the areas.

Another possibility is that the socioeconomic circumstances and the environment per se could be associated with reduced survival[149]. Low social support, low social participation etc. have been associated with

increased cardiovascular mortality[114, 150.] It can be assumed that many of these risk factors are more prevalent in areas with low SES.

Methodological aspects of stroke surveillance

The quality of a stroke register depends on its ability to identify all cases with stroke and on the accuracy of the diagnoses. Both over-inclusion and under-inclusion are potential problems. The case-finding of the STROMA register includes a broad search among patients with neurological symptoms (loss of motor function, vertigo, loss of vision, headache, etc, etc) which could indicate a stroke event. Both hospitalized and non-hospitalised patients are included. The medical records of these patients are searched for previous stroke events and the present and previous episodes are validated according to the stroke criteria.

Our ongoing quality work has shown that very few cases die from stroke outside hospital and that very few cases that fulfil the stroke criteria can be added by using the cause of death register. On the contrary, stroke cases that are included in the cause of death register and not in STROMA are almost exclusively false positive cases. Until 1995, all nursing homes were contacted regularly in order to ensure that all cases had been covered by STROMA. However, it was found that virtually all cases were referred to the hospital, and retrieved by the case-finding procedure at the hospital. The nursing homes were therefore not systematically visited after 1995. One measure of the completeness of the register could be the number of stroke events that are detected, and that should have been detected previously. This number is very small (less than 6 per year) and mainly citizens from Malmö that suffered from stroke abroad or at another hospital in Sweden.

It is almost impossible to guarantee a completeness of 100% retrieval of cases in a stroke register that monitor a large population. However, there are many reasons to assume that the completeness of STROMA is very high. In our opinion, the STROMA register well fulfils the standards of the criteria for stroke registration suggested by Warlow and Malmgren[151, 152].

Studies of stroke incidence also require valid and representative information about the background population. It is well-known that most cohort studies have participation rates below 75%, and that high risk individuals, for example unmarried individuals and individuals with foreign background, often are drop-outs from these studies. In this study, information was available for the entire background population, which is a major strength. We also had information about migration or change in marital status during the follow-up period. We therefore could censor individuals who moved out from Malmö.

The socioeconomic level of the residential areas was assessed by means of a socioeconomic score. Previous studies have shown that this score is associated with incidence of stroke[93] and myocardial infarction[96]; survival after myocardial infarction[95], the prevalence of cardiovascular risk factors[93]. The score was based on the socioeconomic levels in the early 1990, and one question is if the socioeconomic level has changed during the study period. However, the areas with low socioeconomic levels are still the same. We have found that the correlation between the socioeconomic score and the dependency of social support in 2002 was very high ($r>0.92$).

The main limitation of the study is that no information on cardiovascular risk factors, e.g., individual exposure to smoking and hypertension was available. However, to collect these data from an unselected urban population is impossible for practical reasons. Hypertension is generally considered to be the most important risk factor

for stroke in the general population. In a large female cohort from the city, we found no difference in prevalence of hypertension between married and single women[63]. Single women were however more often smokers and had higher plasma lipids. Unpublished data from other large cohorts in the city also support the view that prevalence of hypertension shows small differences between married and unmarried men and women, but those other risk factors, particularly smoking, is higher in those living alone. Several studies from the city have shown that the prevalence of cardiovascular risk factors is associated with the socioeconomic circumstances[93, 147]. Even though the adjustments for income and self-owned home probably picked up much of the differences in traditional risk factors, it is possible that the reduced risk in married men and women partially is explained by a more favourable risk factor profile. Similarly it is possible that traditional risk factors partly explain the increased incidence in some ethnic groups.

Conclusions

- This study demonstrates a seasonal variation of case fatality of stroke with a peak in February and a trough in August-September and these differences reached statistically significance among women.
- The incidence of stroke showed no consistent association with season, month or weekday.
- This study of an urban population show that divorced and widowed men and women have an increased risk of stroke as compared to those who are married.
- Never married men were not exposed to an increased risk. With the exception of older women, the risk of stroke was increased during the first years after divorce or death of spouse.
- The incidence of stroke and stroke subtypes varies widely between immigrants from different countries in this urban population. The differences in stroke incidence observed in this study only partially reflect the pattern of the stroke mortality reported from these countries.
- Long-term survival after stroke is higher among patients from areas having the most favourable socioeconomic circumstances. The reasons for this relation remain to be explored.

Populärvetenskaplig sammanfattning

Epidemiologi är den vetenskap som studerar sjukdomars förekomst och spridning och hur detta varierar över tiden, mellan geografiska områden och mellan grupper av individer definierade i olika termer. I Malmö finns det mycket goda möjligheter att göra epidemiologiska studier av slaganfall (stroke). Dels finns ett register som följt strokeinsjuknandet sedan 1989. Dels har Sverige en tillförlitlig och utförlig befolkningsstatistik som ger oss goda möjligheter att beskriva risken att insjukna i olika befolkningsgrupper. Syftet med denna avhandling har varit att utforska slaganfallssjukdomen i relation till när man insjuknar (årstids- och veckodagsvariation), var man bor och vem man är i termer av civilstånd och födelseland.

För många sjukdomar kan insjuknandet vara högre eller lägre beroende på årstid och veckodag. Tidigare studier av insjuknande i slaganfall har visat motstridiga resultat. Några studier har rapporterat att risken för stroke är högre på vintern, medan andra har funnit att risken är högst på hösten eller våren.

Vid en genomgång av alla nya fall i Malmö mellan 1989-1999 (7129 fall), kunde vi inte se några säkra skillnader i risken att insjukna under olika årstider. Inte heller skilde sig strokeinsjuknandet mellan olika veckodagar. Däremot såg vi att dödligheten efter insjuknandet var högre bland patienter som insjuknat under vintern. Anledningen till att dödligheten är större under vintern är oklar. Bland de möjliga orsakerna kan nämnas att andra sjukdomar oftare skulle kunna komplicera förloppet under vintern, eller att slaganfallen skulle kunna vara svårare under vintern (Paper I).

Många studier har visat att ensamstående (ogifta, frånskilda eller änkor/änklingar) har högre dödlighet än de som är gifta. Den ökade dödligheten tycks innefatta många olika dödsorsaker. Huruvida risken att insjukna i stroke är olika i dessa grupper är endast lite studerat och ingen har tidigare studerat om risken för stroke är ökad de första åren efter skilsmässa eller makes död. Genom att inhämta uppgifter från Folk och Bostadsräkningen 1990 kunde vi studera risken att drabbas av stroke i relation till civilstånd. Vi kunde också studera om skilsmässa eller makes död efterföljdes av en ökad risk för stroke.

Vi fann att frånskilda män och kvinnor hade en ökad risk, liksom änkor/änklingar. Män som aldrig gift sig hade ingen ökad risk. Vi såg också att skilsmässa eller makes död ledde till en ökad risk under de närmast följande åren. (Paper II). Det finns flera möjliga orsakerna till att frånskilda och änklingar har högre risk. Bland annat kan man tänka sig att skilsmässa eller makes död är en stark stressfaktor som kan öka risken för stroke. En annan möjlighet är att livsstilen hos ensamstående ser annorlunda ut, med mer rökning, mindre fysisk aktivitet etc. Fler studier behövs för att utforska orsakerna till det ökade strokeinsjuknandet.

I Malmös befolkning finns stora invandrargrupper. Tack vare den goda befolkningsstatistik som finns i Sverige kan befolkningen beskrivas utifrån födelseland, något som utnyttjades i nästa arbete. Malmös befolkning indelades i invånare födda i Sverige, Danmark, Norge, Finland, Tyskland, fd Jugoslavien, fd Sovjetunionen, Chile, Polen, fd Tjeckoslovakien, Rumänien, Ungern och Kina/Vietnam dvs. de stora invandrargrupperna i Malmö, 1990. Risken att insjukna studerades från 1990 till 2001. Individer födda i Ungern och fd Jugoslavien hade ökad risk för ischemiska stroke (blodpropp i hjärnans kärl), personer från fd Sovjet och Kina/Vietnam hade ökad risk för intracerebral blödning (hjärnblödning), medan finska invandrare hade ökad risk för subaraknoidal blödning (hjärnhinneblöd-

ning). Invånare från Rumänien hade en lägre risk för stroke än infödda svenskar. Resultaten visar att det finns betydande skillnader mellan olika invandrargrupper. Skillnaderna kan återspegla riskfaktorer och beteenden som förvärvats i hemlandet, men de kan också återspegla det faktum att invandrare utgör selekterade grupper som av olika skäl tagit ett beslut att flytta till ett annat land. Det är tänkbart att dessa grupper i vissa fall är sjukare eller friskare än befolkningen i hemlandet och i det nya landet (Paper III).

Tidigare studier i Malmö har visat att risken att insjukna i stroke eller hjärtinfarkt skiljer sig betydligt mellan olika bostadsområden i Malmö. Risken att insjukna är högst i områden med lägre socioekonomisk nivå, dvs i områden med låg sysselsättningsgrad, högt socialbidragsberoende, hög omflyttning och hög andel invandrare. Huruvida den högre risken att insjukna i stroke också motsvaras av en sämre prognos bland de drabbade har inte studerats tidigare. I det fjärde delarbetet studerades dödligheten bland slaganfallspatienter från olika bostadsområden.

I studien, som innefattade 7680 patienter med stroke under perioden 1989-2000, fann vi att dödligheten var störst bland patienter som kom från sämre bemedlade områden. Skillnaderna kunde ses för dödligheten under de första 28 dagarna efter insjuknandet, under första året efter insjuknandet och för dödligheten fram till 31 december, 2001. Det var framför allt på längre sikt (1 år eller mer) och bland patienter under 75 år som skillnaderna var statistiskt säkerställda.

Att prognosen är sämre bland patienter från sämre bemedlade områden skulle kunna bero på att dessa individer får svårare slaganfall, men det finns flera alternativa förklaringar. En möjlighet är att dessa patienter röker i större utsträckning och de har svarare att ta sig till information om hälsofrämjande livsstil eller att följa den blodtrycksbehandlingen som de ordinerats av sina läkare.

Sammanfattningsvis har avhandlingen visat att det finns betydande skillnader i risken att insjukna i stroke mellan individer från olika länder. Likaså skiljer sig risken mellan gifta, ogifta, frånskilda och änkor/änklingar. Prognosen efter ett slaganfallsinsjuknande är sämre bland patienter från mindre bemedlade områden och bland dem som drabbats under vintermånaderna. Däremot har vi inte funnit stöd för hypotesen att risken att insjukna skulle skilja sig mellan olika årstider eller veckodagar.

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