Stroke: Risk Factors and Trends

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"The best time to plant a tree was twenty years ago. The second best time is now"
- Chinese proverb

To my family

ABSTRACT

Stroke is a severe disease that affects 30,000 people in Sweden every year. Three quarters of stroke events are first time events. The risk of premature death and disability is high among stroke survivors. Knowledge about risk factors, trends in incidence and prognosis after stroke is important to reduce the risk and improve the outcome. The aim of this thesis was to investigate the long-term risk of coronary heart disease (CHD) and stroke among men from middle age and extending into old age, temporal trends in ischemic stroke (IS) incidence, and prognosis after stroke among younger IS patients (18-54 years). For this purpose the Primary Prevention (PPS) study was used in Paper I. Data from the Swedish Inpatient Register (IPR) and Cause of Death Register was used in Paper II to IV.

The European SCORE model estimates the 10-year risk of cardiovascular mortality among middle-aged people. This model is based on five risk factors: age, gender, blood pressure, serum cholesterol and smoking status. Paper I showed that the importance of these risk factors differed considerably when estimating the short-term (0-10 years) and long-term (0-35 years) risk of CHD and stroke, such that the prediction was better for CHD than for stroke.

During 1987 to 2010 the incidence of IS decreased among elderly (65-84 years) and middle-aged (45-64 years) people. However, among younger people (18-44 years) the incidence increased about 1.5% per year during the same period of time. From 1987 to 2006 the 4-year mortality risk decreased among young men and women after an IS. Similar findings were observed for recurrent IS. In addition, we observed that most of the decline in recurrence occurred within the first year.

In conclusion, this thesis showed that CHD and stroke differs not only by their clinical manifestations but also by how they were influenced by different risk factors at baseline over an extended follow-up. The risk of IS declined for older but not among young people which is a worrying trend but prognosis after stroke has improved over time among younger IS patients, however, the risk of either death or recurrent IS is still high.

Keywords: SCORE, prediction, CHD, stroke, ischemic stroke, temporal trends, incidences, mortality, recurrent ischemic stroke,

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LIST OF PAPERS

This thesis is based on the following four articles. Each paper is referred by their Roman numerals:

I Giang KW, Björck L, Novak M, Lappas G, Wilhelmsen L, Torén K, Rosengren A. Stroke and coronary heart disease: predictive power of standard risk factors into old age long-term cumulative risk study among men in Gothenburg, Sweden.
Eur Heart J 2013;34(14):1068-1074.

II Rosengren A, Giang KW, Lappas G, Jern C, Torén K, Björck L. Twenty-Four-Year Trends in the Incidence of Ischemic Stroke in Sweden from 1987 to 2010.
Stroke 2013;44(9):2388-2393.

III Giang KW, Björck L, Nielsen S, Novak M, Sandström TZ, Jern C, Rosengren A. Twenty-Year Trends in Long-Term Mortality Risk in 17,149 Survivors of Ischemic Stroke Less than 55 Years of Age.
Stroke 2013;44(12):3338-3343.

IV Giang KW, Björck L, Heden Ståhl C, Sandström TZ, Jern C, Torén K, Rosengren A. Trends in Risk of Recurrence after First Ischemic Stroke Among Younger Adults under 55 Years of Age in Sweden.
In manuscript

CONTENTS

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
AER	Absolute excess risk
AF	Atrial fibrillation
AMI	Acute myocardial infarction
APC	Annual percentage change
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass grafting
CHD	Coronary heart disease
CI	Confidence intervals
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
FRS	Framingham risk score
HF	Heart failure
HR	Hazard ratio
ICD	International Classification of Disease
ICH	Intracerebral Hemorrhage
IPR	Inpatient registry
IS	Ischemic stroke
KM	Kaplan-Meier
LDL	Low-density lipoprotein
NOACS	Novel Oral Anticoagulation
PCI	Percutaneous coronary intervention
PPS	Multifactor Primary Preventive Study
PPV	Positive predictive value
Riks-stroke	The Swedish stroke register
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation
SHR	Subdistribution hazard ratio
SMR	Standardized mortality ratio
SU	Stroke units

INTRODUCTION

Stroke is a prevalent disease and one of the most common causes of death and disability among adults wordwide.[1, 2] More than 6 million people died from stroke in 2012 and among survivors, stroke may have different consequences on physical and cognitive functioning.[3] The number of stroke cases in Sweden has been estimated to about 30,000 persons per year, of which three quarters or 23,000 cases are first time events.[4] The mean age in a first stroke is 75 year but men suffer their first stroke earlier, on average, than women (73 versus 78 years).[5]

Pathophysiology of stroke

Stroke is a condition where oxygen rich blood flow to the brain is being disrupted which causes damages to the brain tissues due to oxygen deficiency (hypoxia). Typical symptoms of stroke may be face dropping, numbness or weakness in the extremities or sudden impairment of vision or speech. To reduce the damage and prevent long lasting disability public knowledge of these symptoms is important to promote immediate healthcare contact. In general, stroke can be divided into two major subtypes: ischemic stroke (IS) and hemorrhagic stroke. A transient ischemic attack (TIA) is a temporary interruption of the blood flow with symptoms lasting less than 24 hours. A TIA is regarded as a warning sign for an upcoming major event. From a medical perspective it is important to distinguish between these conditions since treatment varies depending on the subtype. This is done by organizing a neuroimaging of the brain with either a Computer Tomography (CT) or Magnetic Resonance Imaging (MRI).

Ischemic stroke is the most common subtype in high income countries and accounts for about 80-85% of all stroke cases.[4] Thrombotic and embolic stroke are two causes of IS. A thrombotic stroke will occur if a blood clot (thrombus) forms locally in the cerebral artery and obstructs the blood flow to the brain. This is usually due to atherosclerosis. If the clot originates elsewhere in the circulatory system it is called an embolic stroke. A cardioembolic stroke originates from the heart.

Hemorrhagic stroke accounts for about 15-20% of all stroke cases in most high income countries and occurs when an artery in the brain ruptures. Hemorrhagic stroke can be divided into two different subtypes, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). ICH is caused by a rupture of an artery within the brain while SAH occurs at the surface of the brain. The bleeding damages the cells and neural pathways in the affected area both directly and locally due to the increased pressure and reduced blood flow.

Atherogenesis

Atherosclerosis is a chronic disease that often starts in early life and causes plaque formation in the arteries over time.[6] The process starts when excess low density lipoprotein (LDL) particles enter the endothelium layer and become oxidized (oxLDL). The damage in the artery triggers an inflammatory response that attracts macrophages which consume the oxLDL and slowly become foam cells that appear as fatty streaks.

Eventually, the foam cells die and form a lipid core. A thin fibrous cap made of smooth muscle cells and collagen covers the core or the atheroma (atherosclerotic plaque). Over time the plaque may grow and expand into the lumen which leads to a narrowing of the artery. If a plaque ruptures, a blood clot (thrombus) may occur and obstruct the blood flow. This may cause an acute myocardial infarction (AMI) or a stroke depending on the site of the occlusion. Risk factors such as dyslipidemia, smoking, diabetes, and hypertension all contribute to the atherosclerosis progression.[7, 8]

Risk factors for stroke

Risk factors for stroke can be divided into modifiable and non-modifiable factors. Non-modifiable factors are age, male sex, genetic factors and previous history of cardiovascular disease (CVD).[9] Modifiable risk factors are lifestyle factors such as diet, physical activity, and overweight/obesity, contributing to risk factors such as hypertension, dysglycemia/diabetes and lipid aberrations.[9-13] Another important modifiable risk factor is smoking. Stroke is usually due to a combination of multiple factors.

Age and gender

Stroke can occur at any age, but the risk increases markedly with age, doubling with each decade after the age of 55. At any given age, men have a higher age-specific stroke incidence than women.[9, 14-16]

Diet

Diet pattern has an important role through its impact on other known risk factors for stroke such as hypertension, overweight and cholesterol levels.[17] For example, excess salt intake increases blood pressure while saturated fat has an impact on cholesterol. Previous reports have showed that high consumption of vegetables and fruits reduce the risk of stroke while unhealthy foods (e.g. deep fried and fast food) have an opposite effect.[11, 18-20] However, the INTERSTROKE study did not find any association between consumption of vegetables and decreased risk of stroke.[11]

Total cholesterol

High cholesterol (hypercholesterolemia) is an independent risk factor for ischemic heart disease (IHD) but the relationship to stroke is more complex.[21] Previous studies have failed to find an association between cholesterol and overall stroke risk.[22,23] However, some studies like the Multiple Risk factor intervention study (MRFIT) found an association between higher cholesterol levels and an increased risk of fatal IS.[24] Similar findings were reported in the Asia Pacific Cohort Studies Collaboration (APCSC) study whereas the Eurostroke project did not find any relationship between cholesterol levels and IS.[25, 26] Low cholesterol levels have been found to increase the risk of hemorrhagic stroke in some studies.[27, 28] Therefore, serum cholesterol levels may have a different impact in the different subtypes of stroke.

Smoking

Cigarette smoking is a well-studied lifestyle risk factor for stroke with a clear dose-response relationship between risk and cigarettes smoked per day.[11] The toxic

compounds in tobacco have impact on the atherosclerosis progression.[29, 30] Some studies have found that the relative risk of stroke is approximately two times higher for smokers when compared to nonsmokers.[11, 31] Exposure to passive smoking or environmental tobacco smoke increase the risk of stroke and smoking cessation reduces the risk.[32-35] Intervention against smoking should therefore be a high priority in both primary and secondary prevention of stroke.

Hypertension

The definition of hypertension is a systolic blood pressure (SBP) of ≥140 mmHg or a diastolic blood pressure (DBP) of ≥90 mmHg but lower for patients with diabetes (≥130/≥80 mmHg).[36, 37] Hypertension is a well documented modifiable risk factor for stroke. The risk is strongly correlated to blood pressure (BP) levels.[38, 39] Lifestyle changes such as increased physical activity and change of diet are recommendations to lower overall BP levels and to reduce risk.[40] For patients with diagnosed hypertension, antihypertensive drugs (e.g. angiotensin-converting–enzyme (ACE) inhibitors, diuretics and β-blockers) are recommended in addition to lifestyle changes to reduce the risk of stroke and other vascular events.[41] For example, in a meta-analysis the risk of stroke was reduced by approximately 29% in the treatment group with low-dose diuretics when compared to the placebo group.[42]

Obesity

The prevalence of obesity is increasing in Sweden and is a major health problem that is associated with increased risk of stroke and other CVD.[43] Obesity increases the risk of hypertension, type-2 diabetes and speeds up the atherosclerotic progression.[44, 45] The definition of obesity is a body mass index (BMI) of ≥30 kg/m^2 and of abdominal obesity a waist hip ratio >0.90 in men and >0.85 in women. Some previous studies have found an association between stroke and elevated BMI (>25 kg/m^2) but the relationship of general obesity to incident stroke is weaker than that of abdominal obesity.[46-49] This suggests that both the amount and the distribution of adiposity are important for stroke risk.

Physical activity

Previous studies have shown that physical inactivity is a risk factor for stroke while regular physical activity has a protective effect.[50, 51] The exact intensity or dose-relationship is however not yet understood. Some have showed that moderate to strenuous physical activity reduces the risk of stroke.[50] The protective effect of physical activity is thought to be mediated through reduction in excess body weight, reduced risk of hypertension and other risk factors associated to CVD.[40, 52, 53]

Diabetes

Diabetes is a disorder that occurs when the beta-cells in the pancreas no longer produce insulin (type-1) or become resistant to insulin (type-2). Type-1 diabetes is an autoimmune disorder, generally with onset during childhood and early adulthood, while type-2 diabetes is a metabolic disorder associated with obesity, particularly abdominal obesity, and is a disease of the middle aged and elderly. Previous studies have shown that diabetes independently increases the risk of stroke but there is a lack of evidence that intensive glycemic control reduces the risk of stroke.[54-57]

Stress

The relation between stress and increased risk for stroke has been discussed over the past years and findings on this subject have been inconsistent.[58-61] However, in a recent study by O´Donnell et al psychosocial stress (defined as general stress at home and workplace) increased the risk of stroke by 30%.[11]

Medications and treatments

Primary prevention is arguably the most effective approach to reduce the burden of stroke over time. Promotion of lifestyle changes such as increased physical activity, healthy diet and smoking cessation are important as are recent improvements in treatment of associated conditions such as hypertension, diabetes, and atrial fibrillation.[62,63] In patients with prior stroke secondary prevention aims to reduce the risk of recurrent events and death. This includes both lifestyle changes and the use of medications.

Stroke units

Earlier studies have shown that patients with stroke have better outcome when treated at a stroke unit (SU) compared to a general ward.[64-67] The constituents of a successful SU are a multidisciplinary team focused on stroke care, early management and mobilization, treatment, rehabilitation and continuous education of the staff.[68] According to a recent report from the Swedish stroke registry (Riks-stroke) 90% of stroke patients are now treated at a SU.[5]

Antihypertensive medication

In both primary and secondary prevention, treatment of hypertension should be regarded as a top priority. The risk of stroke is associated to both SBP and DBP levels e.g. a reduction of 10 mmHg in SBP reduces the risk of a first time stroke by one third.[39] In a primary prevention setting the use of antihypertensive agents such as ACE-inhibitors and diuretics reduces the risk of stroke and other vascular events.[69,70] Similar effects have also been observed in secondary prevention of stroke.[71, 72] The Perindopril Protection Against Recurrent Stroke study (PROGRESS) showed that a combination therapy with ACE-inhibitor (Perindopril) and diuretic (Indapamide) had better effect in secondary prevention against recurrent stroke when compared to a monotherapy.[73]

Antiplatelet medication

Antiplatelet drugs inhibit the formation of blood clots (thrombus) by targeting the platelet. In patients with previous stroke or TIA, the use of antiplatelet therapy (e.g. aspirin) have been estimated to reduce the risk of stroke and other vascular events by about one quarter (22%).[74] Aspirin is a common and inexpensive medication often used in secondary prevention in stroke, reducing the risk of recurrent stroke but is associated with an increased risk of hemorrhagic stroke.[75, 76] A combination treatment with dipyridamole has been reported to be more effective than monotherapy but is less well tolerated by patients.[77, 78] Clopidogrel is similar to aspirin but combination therapy with clopidogrel and aspirin did not show any improvement over clopidogrel

alone.[63] However, the risk of major hemorrhagic stroke was higher in the combination therapy than the monotherapy group.

Anticoagulation

Anticoagulation drugs actively prevent the coagulation of blood and have proven to be more effective than the use of antiplatelet therapy such as aspirin in prevention of cardioembolic stroke.[63, 79] However, the risk of bleeding is also greater.[80] Therefore, anticoagulation drugs should only be prescribed to patients with known cardioembolic cause (e.g. atrial fibrillation). Warfarin reduces the risk of stroke when compared to placebo group in randomized controlled trials, but needs to be strictly monitored.[79] Novel Oral Anticoagulation (NOAC) drugs have been proven to be effective in primary and secondary prevention and patients treated with NOACS has lower risk of bleeding and do not need to be closely monitored as with Warfarin.[81-85]

Lipid drugs

Lipid concentration like LDL-cholesterol is strongly associated to the risk of AMI but the relation to stroke is more complex. The knowledge about the benefits of statin as a secondary prevention against recurrent stroke is limited. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial (SPARCL) a high dose of atorvastatin in patients with recent stroke or TIA led to a 16% reduced risk of recurrent stroke after a follow-up time of 4.9 years when compared to placebo.[86] However, a slight increase in hemorrhagic stroke was reported in the treatment group. Guidelines in secondary prevention recommend the use of statin in patients with prior stroke of known atherosclerotic origin.[63]

THE RATIONALE OF THE THESIS

Stroke is a disease that may occur at any age and is often due to a combination of multiple risk factors. The risk of death or recurrent stroke is highest within the first year.[2,4] The outcome depends on several factors such as stroke severity, subtype, treatments and previous medical conditions (e.g. diabetes or hypertension).[2] This thesis focuses on the risk of coronary heart disase (CHD) and stroke based on individual risk factors over a long period of time, temporal trends in IS incidence and prognosis after stroke over a 4 year period.

To create awareness about CVD it is sometimes more useful to present risk charts. For this purpose different system based on statistical models have been developed. These models often estimate individual risk of having a CVD event by using certain risk factors and criteria. The Framingham risk score model uses data from the Framingham heart cohort study that primarily consists of North-American residents from the town of Framingham in Massachusetts.[87] This model estimates the 10-year risk for an individual to develop a CVD event defined as CHD, cerebrovascular events, peripheral disease and heart failure.[88] Since the Framingham score models are based on Americans, albeit of Caucasian origin, it was not considered to be representative for Europe that consists of more diverse populations and cultures. As a result, the Systematic Coronary Risk Evaluation (SCORE) chart was developed in 2003, estimating the 10-year risk of CVD (including CHD and stroke) on an individual basis based on five risk factors: gender, age, smoking status, serum cholesterol and SBP.[89] Data from 12 European countries (including Sweden) were used for the development of this model which is considered to be more representative for European conditions than e.g. the Framingham risk score (FRS). However, unlike the FRS the European model uses fatal events to predict the 10-year risk for a population up to 65 years of age which may limit the predictability of nonfatal events. In addition, the SCORE model focuses on CHD and stroke simultaneously and these two outcomes may differ considerably in predictability over time. To address these issues we investigated the risk of CHD and stroke separately based on the risk factors from the SCORE model.

For the past decades, stroke incidences has decreased in high income countries but the absolute number of cases is expected to increase in the future due to a growing number of people and elderly in the population.[90] One study based on the Swedish Inpatient Registry (IPR) showed that hospitalization of stroke increased from 1989 to 2000 among people aged 30 to 65 years.[91] Increasing incidence among younger people has also been observed in the United States.[92] A marked decline in IS mortality was observed in the Netherlands between 1987 to 2005 but with a stable or slightly increase in stroke incidence.[93] In Sweden, there is a lack of nationwide studies on continuing trends in the incidences of stroke among different age groups after the year 2000.

Survival after stroke has improved during the last decades. Nevertheless, many stroke survivors still have an impaired prognosis when compared to a healthy population.[94] Most studies on prognosis such as mortality and recurrence after stroke are based mainly on patients older than 55 years of age because a majority of stroke victims are elderly. Findings from these reports may not always be applicable to younger patients.

Therefore, knowledge about prognosis among younger adults with a first time stroke is important because they stand to lose more of their remaining lifetime compared with older patients. Today, there are few studies with a sufficient number of younger stroke patients that can investigate trends in mortality and recurrent stroke over an extended period of time.

AIMS

The aim of this research project is to investigate the risk of CHD and stroke separately over a long period of time, temporal trends in incidence and prognosis after stroke among younger IS patients. The specific aims are:

Paper I To investigate the risk of CHD and stroke separately from middle to old age over a 35-year follow-up in a cohort of men by their risk factor status at baseline.

Paper II To investigate age-specific trends in stroke incidence over time in Sweden from 1987 to 2010.

Paper III To investigate trends in mortality risk among younger IS patients (<55 years) in Sweden from 1987 to 2006.

Paper IV To investigate trends in risk of a recurrent IS among younger stroke patients (<55 years) in Sweden from 1987 to 2006.

METHODS

Overview

The individual studies are either based on the Multifactor Primary Prevention study (PPS) cohort or the Swedish IPR and Cause of Death Register (Table 1). All studies were approved by the regional ethical board of Gothenburg. Personal identifiers in registers were replaced by a sequential number to ensure anonymity.

Table 1. Overview of the different research designs

Study	I	II	III	IV
Design	Cohort study	Register based study	Register based study	Register based study
Data collection	The PPS	IPR/Cause of death register	IPR/Cause of death register	IPR/Cause of death register
Inclusion criteria	No previous history of CHD, stroke or diabetes and with a complete data set	Patients aged 18-84 years with a first time IS from 1987 to 2010.	Patients aged 18-54 years with a first time IS and survived for at least 28 days from 1987 to 2006	Patients aged 18-54 years with a first time IS and survived for at least 28 days from 1987 to 2006
Sample size	7,174	391, 081	17,149	17,149
Outcome	Risk of CHD and stroke	Incidence of IS	All cause mortality in IS patients	Risk of recurrent IS
Statistical methods	Competing risk regression	Joinpoint regression	SMR and Cox proportional regression	Cox proportional regression

PPS= The Multifactor Primary Prevention study, IPR= Swedish In Patient Register; SMR= Standardized mortality ratio

Cohort and registries

The Multifactor Primary Prevention study

The Multifactor Primary Prevention study (PPS) started in 1970 as an intervention trial in Gothenburg against smoking, hypertension and hypercholesterolemia.[95] The study included middle-aged men born in 1915 to 1925 with the exception of those who were born in 1923 (because of participation in another study). Participants were aged between 47 to 55 years at baseline (mean age 51) in 1970 to 1973. A third of all men in the city in this age bracket, or 10,000 men were randomly selected as an intervention group. The remaining two thirds were divided into two separate control groups. A postal questionnaire with a letter of invitation was sent to all men in the intervention group. Those who responded to the questionnaire were invited for a first baseline screening to identify and treat risk factors such as hypercholesterolemia, severe hypertension or heavy smoking habits in which 7,495 men took part. Those who did not respond were sent up to three reminders.[95] A first re-examination of the intervention group (n=7517) and a subsample (n=826) of one of the control groups was performed after 4 years. A second and final examination was performed after 10 years in a 20% random subsample of the intervention and control group. There were no significant differences in risk factors levels for serum cholesterol, BP and smok-

ing status between the intervention and control group after 10 years, nor were there any significant differences in major outcomes after the first 11.8 years follow-up. The intervention group was therefore considered as being representative of the general population (Figure 1).

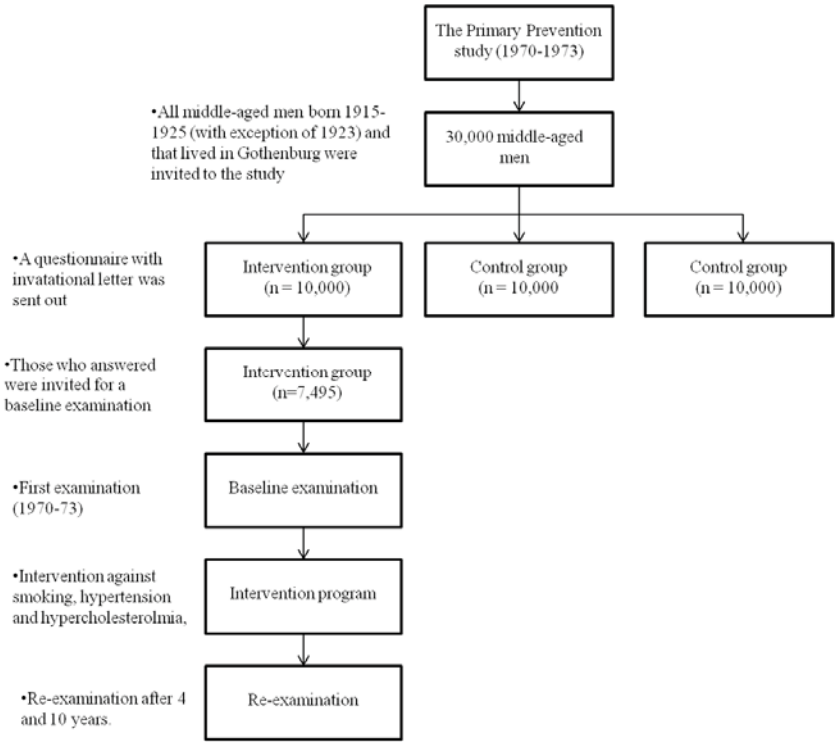

Figure 1. The selection process of the Multifactor Primary Prevention trial.

The screening examination took place during the afternoon. BP was measured after 5 minutes rest (seated). Serum cholesterol levels were taken from blood samples after at least 2 hours fasting. BMI was calculated as weight divided by height (kg/m^2). In total, six categories of BMI were defined in the PPS study: <20, 20-22.5, 22.5-25.0, 25.0-27.5, 27.5-30.0 and >30.0. Information on smoking habits, physical activity, psychological stress and previous history of CHD was collected from the questionnaire. Smoking habits were coded as nonsmoker, former smoker, smoking 1-14 g/day, smoking 15-25 g/day, or more. One cigarette was considered to contain 1 g, a cigarillo 2 g and a cigar 5 g of tobacco. Reported physical activity at leisure and at work was categorized into four separate levels with 1) denoting sedentary work or leisure activity, 2) moderate activity for at least 4 hours a week, 3) regular activity and 4) heavy work or strenuous leisure activity. Psychological stress was defined as feeling tense, irritable or nervous or having sleeping difficulties and was graded as 1) never experienced stress, 2) experienced some periods of stress, 3) experienced some period of stress during the last five years, 4) experienced several periods of stress during the last five years, 5) permanent stress during the last year, 6) permanent stress during the last

five years. Previous history of CVD (e.g. stroke and AMI) was also collected from the questionnaire.

Inpatient Register

The Swedish inpatient register (IPR) or Hospital discharge register was first established in 1964 by the National Board of Health and Welfare (Socialstyrelsen). In the beginning, only data from patients with somatic diseases was collected from a few counties in Sweden. This expanded over time and from 1987 the IPR has been operating on a nationwide basis collecting both somatic and psychiatric diagnoses. All hospitals are required to report principal and contributory discharge diagnoses to the IPR. Several studies have investigated the quality and validity of the diagnosis in the IPR. In a recent study Ludvigsson et al showed that the positive predictive value (PPV) was 85% to 95% for a range of major diagnoses.[96] For the purpose of the studies included in this thesis data from the IPR and Cause of Death Registers were linked using the unique 10-digit Swedish personal identifier. Diagnoses were coded according to the International Classification of Diseases (ICD), ICD-8 from 1968 until 1987, ICD-9 from 1987 until 1996 and ICD-10 from 1996 and onwards.

The Cause of Death Register

The Cause of Death Register has been in operation since 1961 and includes all deaths among Swedish residents. The register is based on national death certificates. In 2008 the number of missing certificates was estimated to 0.8% and another 2.7% were insufficiently recorded. Validation of diagnosis in the Cause of Death Register is generally high for ischemic heart disease but lower for stroke.[97, 98]

Study populations and methods

Paper I

The first paper is a cohort study based on the PPS. Baseline information (1970-73) was used from individuals in the intervention group. A total of 7,149 men aged 47 to 55 years with no previous history of CHD, stroke or diabetes and with a complete data set were included in the study. The International Classification of Disease was used to identify non-fatal and fatal events of CHD and stroke. CHD was defined by the following discharge codes 410 (ICD-8, 9) and I21 (ICD-10). Stroke was defined by 431,433, 434, 436 (ICD-8, 9) and I61-I64 (ICD-10).

The follow-up was extended through 2008 to estimate the short-term (0-10 years) and long-term (0-35 years) risk of CHD and stroke. End points of first time events were registered from several sources. For individuals up to 65 years of age, both CHD and stroke were recorded using criteria from the local CHD and stroke registers.[99, 100] Case records for all hospital diagnosis were checked manually by one nurse and one medical technician from the start of the study. In addition, all hospital discharge codes from Gothenburg have been reported to the national registries since 1970 with exception of 1976 due to legislative changes for that single year. A file of all participants were run against the national hospital discharge register and matched against the Cause of Death Register.

Definitions of risk factors and groups

To estimate the risk of CHD and stroke the following risk factors was used: SBP, DBP, serum cholesterol, hypertension, antihypertensive treatment and smoking status. Hypertension was defined as a SBP of >140 or DBP >90 or if an individual received hypertensive treatment. Non-smokers were defined as never smoker or being a former smoker (>1 months without smoking) and the rest as current smokers. Since the mean levels of SBP and serum cholesterol were high compared with current optimal levels for SBP and serum-cholesterol were defined at a higher cut-off point than would currently have been the case today. This was also done to create sufficiently large groups. All men were stratified into one of five groups based on the number of risk factors at the baseline investigation:

- Optimal risk: SBP <140 mmHg without antihypertensive treatment, and serum cholesterol <5.0 mmol/L, and non-smoker.
- Low risk: SBP 140-159 mmHg without antihypertensive treatment and/or serum cholesterol 5.0-5.9 mmol/L and non-smoker.
- Moderate risk: SBP ≥160 mmHg or antihypertensive treatment or serum cholesterol ≥6.0 mmol/L or current smoker (at least one major risk factor)
- Elevated risk: SBP ≥160 mmHg or antihypertensive treatment and/or serum cholesterol ≥6.0 mmol/L and/or current smoker (at least two major risk factors)
- High risk: SBP ≥160 mmHg or antihypertensive treatment and serum cholesterol ≥6.0 mmol/L and current smoker (all risk factors present).

Figure 2 shows the distribution of all men into different risk groups. The low risk group was used as the reference group.

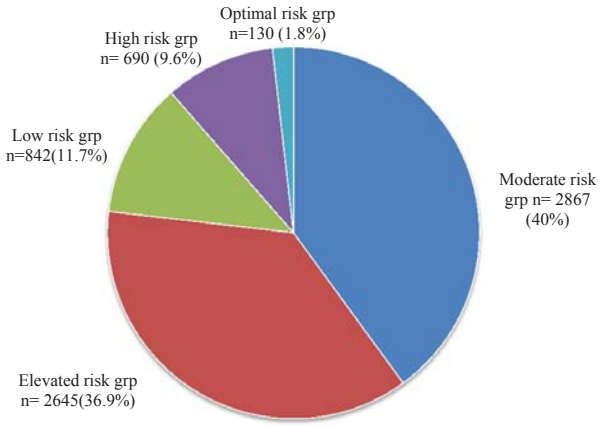

Figure 2. Distribution of men in the different risk groups in the PPS.

Paper II-IV

In Paper II to IV the IPR and Swedish Cause of Death Register were used to estimate trends in the incidence rate of IS and prognosis after hospitalization. Ischemic stroke was defined by the following hospital discharge codes: 434,436 (ICD-8,9) and I63,I64

(ICD-10). Data from 1980 and onwards was used in order to ensure that only first stroke events were included, after a uniform time frame of 7 years. This was done for each separate year from 1987 to 2010 in Paper II and from 1987 to 2006 in Papers III and IV. Neuroimaging (computerized tomography scans) was standard procedure in suspected stroke cases throughout the study period.

Paper II included all patients aged 18 to 84 years who were discharged for the first time with an IS or who died outside hospital during 1987 to 2010 with a stroke as a principal or underlying diagnosis. Over a 24-year period 391,081 incident cases of IS were identified. Comorbidities were defined by the following hospital discharge codes (main or contributory diagnostic codes): Diabetes: 250 (ICD-8 and ICD-9), E10, E11, E14 (ICD-10); hypertension: 401-405 (ICD-8 and 9), I10-I15 (ICD-10); AMI: 410 (ICD-8 and 9), I21 (ICD-10); IHD: 410-414 (ICD-8 and 9), I20-I25 (ICD-10); atrial fibrillation (AF): 427.92 (ICD-8), 427D (ICD-9), I48 (ICD-10); and cancer: 140-239 (ICD-8 and ICD-9), C00-D48 (ICD-10).

Paper III and IV included all patients with a first time IS aged 18 to 54 years who survived for at least 28 days after hospitalization from 1987 to 2006 (Figure 3). Over that time period 17,149 IS patients were identified. All patients were stratified into four time periods according to admission period: 1987 to 1991, 1992 to 1996, 1997 to 2001 and 2002 to 2006. In Paper III patients were followed for 4 years with regard to all cause mortality. In Paper IV they were followed at time intervals of 1 to 6 months, 6 to 12 months, 1 to 2 years, 2 to 3 years and 0 to 4 years with regard to recurrent IS.

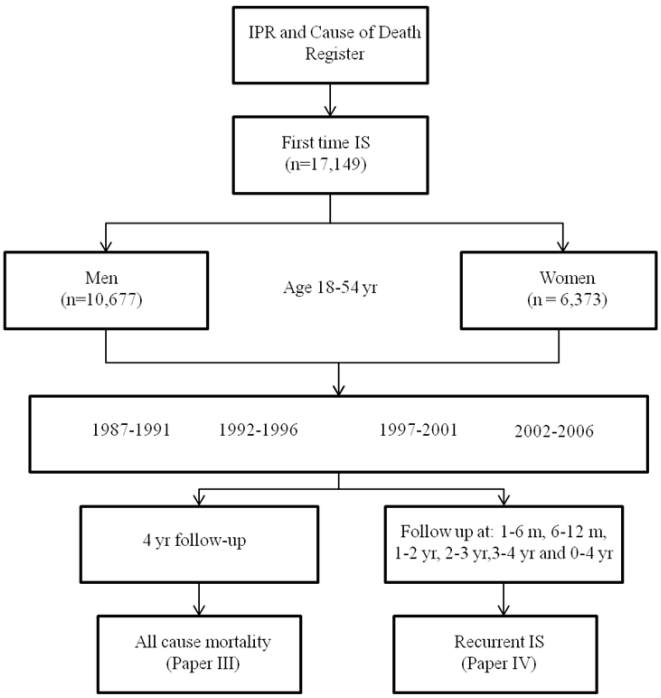

Figure 3. Population selection and outcomes for Paper II and III.

Recurrence was defined as either a fatal (death in hospital) or non-fatal event that occurred at least 28 days after index hospitalization and with at least 2 days between discharge from hospital to the next admission (Figure 4). The main author (K.W.G) and a stroke physician (C.H.S) reviewed separately a subsample of all cases (100 cases) to ascertain that the selection process was appropriate, particularly with respect to the potential admission for the index stroke into a rehabilitation unit.

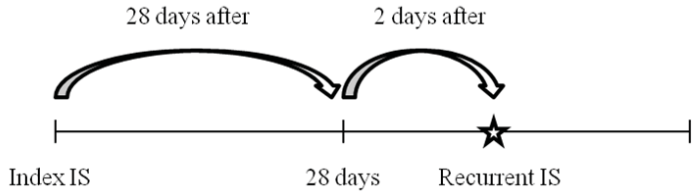

Figure 4. Selection criteria for recurrent IS.

The following main or contributory diagnostic codes were used to define comorbidities: AF: 427.92 (ICD-8), 427D (ICD-9), I48 (ICD-10); CHD: 410-414 (ICD-8, 9), I20-I25 (ICD-10); heart failure (HF): 427.00, 427.10 (ICD 8), 428 (ICD-9), I50 (ICD-10); hypertension: 401-405 (ICD-8, 9): I10-I15 (ICD-10); malignancy: 140-208 (ICD-8, 9), C00-C97 (ICD-10); congenital heart disease: 746-747 (ICD-8), ICD-9: 745-747 (ICD-9), Q20-Q26 (ICD-10); valvular disease: 394-397 and 424 (ICD-8,9), I05-I09, I34-I35(ICD-10); diabetes: 250 (ICD-8,9), E10-E14 (ICD-10; cardiomyopathy: 425 (ICD-8,9, I42 (ICD-10); chronic respiratory disease: 490-496 (ICD-8,9), J40-J47(ICD-10). Surgical treatment was defined by the following surgical codes: Coronary artery bypass grafting (CABG): 3066, 3067, 3105, 3127, FNA, FNB, FNE, FNC; percutaneous coronary intervention (PCI): 3080, FNG 00, FNG 02, FNG 05. In Paper IV, IHD was defined as CHD, PCI or CABG. Cause specific deaths in Paper III were defined as: subarachnoid hemorrhage: 430 (ICD-8,9), I60 (ICD-10); IS: 434 (ICD-8,9), I64 (ICD-10); hemorrhagic stroke: 431, 432 (ICD-8,9), I61, I62 (ICD-10); any other stroke diagnosis: 433, 436–438 (ICD-8,9), I64–I68 (ICD-10); CHD: 410–414 (ICD-8,9), I20–I25 (ICD-10); CVD: 390–459 (ICD-8,9), I00–I99 (ICD-10); malignancy: 140–208 (ICD-8,9), C00–C97 (ICD-10).

Statistical analyses

Descriptive and analytical statistics were used to estimate prevalence and mean values. To compare differences in categorical variables chi-square tests (χ^2) were used and Cochran-Armitage test for trend. Regression models were applied to estimate changes in risk over time. All statistical analyses were performed either with SAS version 9.3 (SAS Institute, Cary, NC, USA) or R version 2.15.1.

Paper I

To analyze the long-term risk of CHD and stroke among middle-aged men it was necessary to adjust for competing risk which occurs when one type of outcomes precludes the main risk of interest (e.g. death). Therefore, it is important to apply a statistical

model that accounts for competing events that could potentially end the follow-up for a study subject in such a way that it violates the random censoring when calculating risk differences in risk factors and groups. To calculate the risk of CHD and stroke, a modified Cox proportional risk regression model as described by Fine JP and Gray RJ was used in a competing risk setting.[101, 102] From the competing risk regression the age-adjusted subdistribution hazard (SHR) with two-sided 95% Confidence Interval (CI) was estimated for individual risk factors and groups were each categorized risk level was compared with the corresponding reference group. R-package "cmprsk" was used to calculate SHR and cumulative risk. The program is publicity available at the R archive network site for free.

Paper II

A direct standardization with the Swedish population (2010) was used to estimate the age-standardized incidence rates per 100,000 person years. Cochran-Armitage trend tests were used to assess trends in 1-year mortality. To investigate changes in incidence and mortality over time a joinpoint regression was used (Joinpoint Regression Program version 3.3.1, Statistical Research and Applications Branc, National Cancer Institute). This method estimates trends as the annual percentage changes (APCs) over time intervals and then attempts to identify specific time points where significant changes in these trends occurred. The age-standardized annual rates were then fitted in a log-linear autoregressive model, and the number of possible joinpoints was set between 0 to 3. The variance of the standardized rates was estimated according to the fact that these are the weighted sum of Poisson variables. For each estimate of mean APC, 95% confidence intervals were calculated.

Paper III

Standardized mortality ratios (SMR) were used to compare mortality rates in patients with a first time IS with those in the general population and was calculated as the ratio of the observed number of deaths to the expected number of deaths with two-sided 95% CIs. The expected mortality in the general population was calculated on the basis of age, sex and calendar year from the mortality rates from the Official Statistics of Sweden (SCB). The absolute excess risk (AER) was derived as the difference between observed and the expected deaths divided by person-years at risk, multiplied by 100. A Cox proportional hazard regression was used to estimate age-and sex-specific changes in mortality over time. The first period (1987-1991) was used as reference and all final models were adjusted by age, diabetes and tested for proportionality by interaction of the covariates age, diabetes and time in order to adjust for non-proportionality. Survival after stroke was estimated by Kaplan-Meier (KM) method with log-rank to test if there were any changes in survival between time periods.

Paper IV

Baseline characteristics are presented with regards to proportions and percentages for each individual comorbidity, gender and time period. A Cochran-Armitage test was used for trend analysis over time, a p-value of ≤ 0.05 was considered as significant. Incidence rate for recurrent IS was calculated as the number of individuals having a recurrence divided by total follow-up time for each time intervals 1 to 6 months, 6

to 12 months, 1 to 2 years, 3 to 4 years and 0 to 4 years. A Cox proportional hazard regression with 95% CI was used to calculate changes in the risk of recurrent IS over time. The first period (1987-1991) was used as reference; all final models were adjusted for age and tested for proportionality by interaction of age and time to adjust for non-proportionality. Stroke free survival (defined as free from recurrent IS and death) was estimated with KM.

RESULTS

Stroke and coronary heart disease: predictive power of standard risk factors into old age long-term cumulative risk study among men in Gothenburg, Sweden (Paper I).

The aim of the first paper was to investigate short-term and long-term risk of a first time stroke or CHD based on the risk factors from the SCORE model. From the PPS cohort study a total of 7,174 participants free from previous history of CHD, stroke, diabetes and with a complete data set were included. Over the past 35 years 3,752 first events of either CHD or stroke occurred. Of these 2,417 (33.7 %) were a first time CHD and 1,335 (18.6%) a first time stroke.

Long-term effect of individual risk factors

For the individual risk factors (Table 2) the age adjusted SHR after 35-years of follow-up showed that high serum cholesterol (SHR 1.93, 95% CI 1.65-2.26 for serum cholesterol of ≥7 mmol/L, compared to <5.0mmol/L), high SBP (SHR 1.68, 95% CI

Table 2. A 35 year follow-up with subdistribution hazard ratio (SHR) (95% CI) adjusted for age for CHD and stroke with regard to individual risk factors at baseline

Risk factors	Number at risk	Events[a]	Total Observation years	IRR[b] (95 % CI)	Adjusted SHR[b] (95 % CI)
CHD					
Serum cholesterol					
<5.0 mmol/L	703	180	18000	1 (Ref)	1 (Ref)
5.0-5.9 mmol/L	1986	543	51090.5	1.08 (0.91-1.27)	1.10 (0.93 -1.30)
6.0-6.9 mmol/L	2364	818	57901.9	1.45 (1.24–1.71)	1.50 (1.28–1.76)
≥7.0 mmol/L	2121	876	48799	1.86 (1.58-2.19)	1.93 (1.65–2.26)
SBP					
<140 mmHg	2552	692	66570.9	1 (Ref)	1 (Ref)
140-159 mmHg	2573	878	63377	1.31 (1.18–1.45)	1.31 (1.19–1.45)
≥160 mmHg	2049	847	45843.5	1.72 (1.55–1.90)	1.68 (1.52–1.86)
Smoking					
Non-smoker	3577	1112	95528.8	1 (Ref)	1 (Ref)
Smoking	3597	1305	80262.6	1.38 (1.27–1.49)	1.26 (1.16–1.36)
Hypertension					
Non-hypertensive	2171	568	57501.2	1 (Ref)	1 (Ref)
Hypertensive	5003	1849	118290	1.54 (1.40–1.69)	1.51 (1.38–1.66)
Antihypertensive medication	367	166	7794.7	1.56 (1.33–1.83)	1.55 (1.31–1.82)
Stroke					
Serum cholesterol					
<5.0 mmol/L	703	128	18031.4	1 (Ref)	1 (Ref)
5.0-5.9 mmol/L	1986	353	52106.9	0.97 (0.79-1.18)	0.99 (0.81-1.21)
6.0-6.9 mmol/L	2364	457	60870.4	1.09 (0.89-1.32)	1.09 (0.90-1.33)
≥7.0 mmol/L	2121	397	52590.5	1.10 (0.90-1.35)	1.06 (0.87-1.30)
SBP					
<140 mmHg	2552	418	68831.8	1 (Ref)	1 (Ref)
140-159 mmHg	2573	468	66617.5	1.13 (0.99–1.29)	1.11 (0.97-1.26)
≥160 mmHg	2049	449	48149.9	1.48 (1.29–1.69)	1.37 (1.20–1.57)
Smoking					
Non-smoker	3577	715	98698.1	1 (Ref)	1 (Ref)
Smoking	3597	620	84901.1	0.99 (0.89-1.11)	0.86 (0.77-0.95)
Hypertension					
Non-hypertensive	2171	341	59374.1	1 (Ref)	1 (Ref)
Hypertensive	5003	994	124225	1.35 (1.19–1.53)	1.28 (1.13–1.44)
Antihypertensive medication[c]	367	85	8131.4	1.43 (1.15–1.79)	1.31 (1.05–1.65)

[a]First ever occurrence of a CHD or stroke. [b]Age adjusted incidence ratio (IRR) and subdistribution hazard ratio (SHR).
[c]Non-antihypertensive medication vs antihypertensive medication.

1.52-1.86 for SBP of ≥160 mmHg compared to <140 mmHg), current smoking (SHR 1.26, 95% CI 1.16-1.36 for smoker compared to non-smoker), hypertension (SHR 1.51, 95% CI 1.38-1.66 for hypertensive compared to non-hypertensive) and antihypertensive treatment (SHR 1.55, 95% CI 1.31-1.82 for non-antihypertensive medication compared to antihypertensive medication) had increased risk of CHD at baseline. Corresponding results for stroke was high SBP (SHR 1.37, 95% CI 1.20-1.57 for SBP of ≥160 mmHg compared to <140 mmHg), hypertension (SHR 1.28, 95% CI 1.13-1.44 for hypertensive compared to non-hypertensive) and antihypertensive treatment (SHR 1.31, 95% CI 1.05-1.65 for non-antihypertensive medication compared to antihypertensive medication) at baseline were associated with increased risk. High serum cholesterol was not significantly related to stroke and current smokers had decreased risk.

Effect of risk groups

After adjusting for age and competing risk the SHR showed that for each additional risk factor at baseline the risk of CHD increased but a similar trend was not observed for stroke (Table 3). Those individuals with several risk factors at baseline had a SHR of 2.89 (95% CI: 2.41-3.47) for CHD and 1.21 (95% CI: 0.96-1.53) for stroke when compared to the low-risk individuals.

Table 3. A 35-year follow-up with subdistribution hazard ratio (95% CI) adjusted for age for coronary heart disease and stroke with regard to risk groups

Risk groups	Number at risk	Events[a]	Total Observation years	IRR[b] (95 % CI)	Adjusted SHR[b] (95 % CI)
CHD					
Risk groups[b]					
Optimal risk	130	20	3855.6	0.77 (0.49-1.23)	0.69 (0.44-1.07)
Low risk	842	184	24047.7	1 (Ref)	1 (Ref)
Moderate risk	2867	877	74150	1.54 (1.31–1.80)	1.48 (1.27–1.73)
Elevated risk	2645	1001	60530.8	2.16 (1.84–2.52)	2.01 (1.73–2.35)
High risk	690	335	13207.3	3.22 (2.69–3.86)	2.89 (2.41–3.47)
Stroke					
Risk groups[b]					
Optimal risk	130	24	3760.2	1.12 (0.72-1.72)	1.10 (0.72 -1.70)
Low risk	842	144	24429.2	1 (Ref)	1 (Ref)
Moderate risk	2867	535	76677.2	1.18 (0.98-1.42)	1.10 (0.92-1.32)
Elevated risk	2645	494	64196	1.30 (1.08–1.56)	1.12 (0.93-1.35)
High risk	690	138	14536.6	1.56 (1.24–1.97)	1.21 (0.96-1.53)

[a]First ever occurrence of a CHD or stroke. [b] Age adjusted incidence ratio (IRR) and subdistribution hazard ratio (SHR)

In addition, the 10-year and 35-year cumulative risk for CHD and stroke were separately estimated based on the different risk groups. For the first 10 years individuals in the high risk group had an 18.1% risk of developing CHD compared to 1.3% for those in low risk group. Corresponding results for stroke were 3.2% and 0.5% after 10 years. To estimate the long-term effect the follow-up time was extended to 35 years. The risk of CHD was 47.8% among those individuals with adverse levels of risk factors (high risk) compared to 19.6% for stroke (Figure 5).

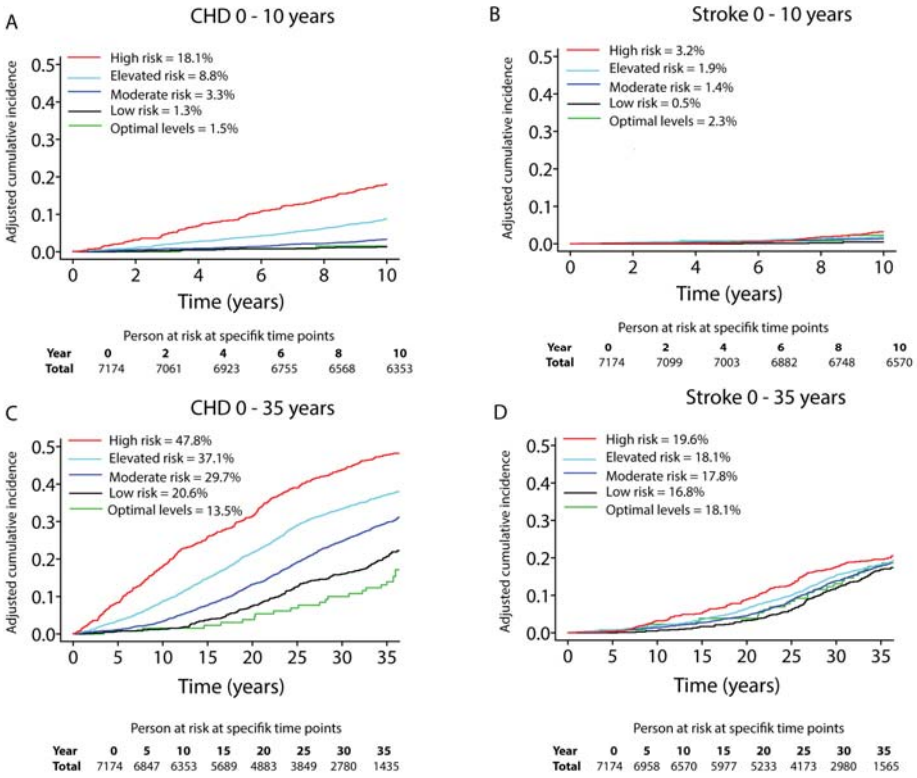

Figure 5. Cumulative incidence curves adjusted for competing risk of death by different risk groups for coronary heart disease and stroke, respectively. The 10-year cumulative risk for (A) Coronary heart disease, B) stroke and the 35-year cumulative risk for (C) coronary heart disease, and (D) stroke.

Twenty-four-year trends in the incidence of ischemic stroke in Sweden from 1987 to 2010 (Paper II)

In this paper a total of 391,081 incident cases of IS were identified from 1987 to 2010 among people aged 18 to 84 years. The mean age of the population was 72.5 years, 1.6% were 18 to 44 years, 16.7% were 45 to 64 years and a majority, or 81.7%, were 65 to 84 years. From the first (1987-1992) to the last 6-year period (2005-2010) the mean age decreased from 73.0 years to 71.7 years. The proportion of patients with diabetes increased from 16.9% to 19.0% whereas diagnostic codes for hypertension increased markedly from 19.1% to 50.7%.

Trends in the incidence of ischemic stroke and mortality during 1987 to 2010

Table 4 shows the trends in incidence and 1-year case-fatality of IS. A continuous increase in stroke incidence was observed from the first (1987-1992) to the last 6-year period (2005-2010) in men and women aged 18 to 44 years. The incidence rate for those aged 45 to 54 years increased from 51.3 to 61.4 per 100,000 person-years over

Table 4. Incidence of ischemisc stroke per 100 000 person-years in Sweden during 1987-2010 by age group and period

Age group (y)		1987–1992	1993–1998	1999–2004	2005–2010
18–44	Rate/100 000 person-years	7.17	8.13	8.26	9.55
	No of cases	1402	1565	1565	1864
	Died within a year, n (%)	141 (10.1)	122 (7.8)	98 (6.3)	86 (4.6)
45–54	Rate/100 000 person-years	51.3	64.1	63.7	61.4
	No of cases	3182	4774	4629	4350
	Died within a year, n (%)	338 (10.6)	328 (6.9)	289 (6.2)	235 (5.4)
55–64	Rate/100 000 person-years	188	221	208	189
	No of cases	9620	11511	13353	13696
	Died within a year, n (%)	1511 (15.7)	1249 (10.9)	1231 (9.2)	1119 (8.2)
65–74	Rate/100 000 person-years	606	689	614	503
	No of cases	30414	32979	27459	24867
	Died within a year, n (%)	7356 (24.2)	6187 (18.8)	4446 (16.2)	3446 (13.9)
75–84	Rate/100 000 person-years	1568	1705	1523	1278
	No of cases	50063	57516	53312	42960
	Died within a year, n (%)	20843 (41.6)	19644 (34.2)	16344 (30.7)	12384 (28.8)

All p for trends in 1-year mortality <0.0001

time, a plateau in the incidence was observed in the second period (1993-1998) but decreased slightly through the last period. A similar pattern was evident for those aged 55 to 64 years but among those aged ≥65 years a distinct peak was found in the second period after which rates started to decline markedly. Figure 6 shows the crude relative yearly changes from 1987 to 2010.

Figure 6. Relative percentage change in the incidence of ischemic stroke by sex and age group in people aged 18-84 years in Sweden from 1987 to 2010. Incidence of ischemic stroke in 1987 was set at 100%, and subsequent percentages are in relation to that year.

Despite an increase of incidence rate of IS among younger patients the overall age-standardized mortality from IS stroke decreased in men and women from 1987 to 2010 (Figure 7), with a more marked decline after the mid-to late 1990s.

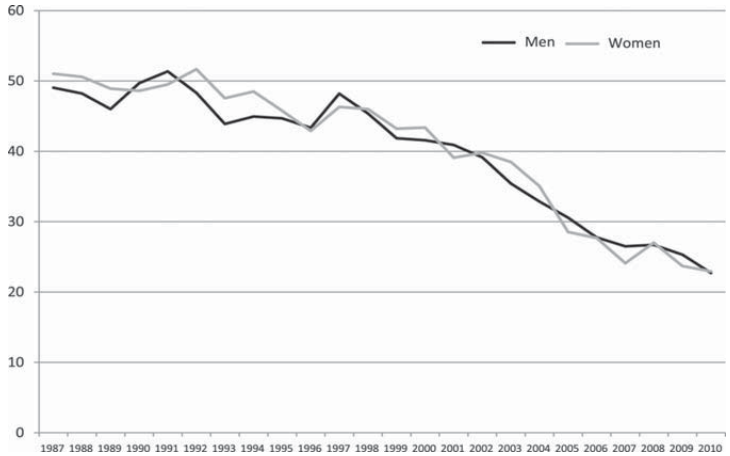

Figure 7. Age-standardized mortality per 100 000 person-years from ischemic stroke in people aged 18-84 years in Sweden from 1987 to 2010.

Joinpoint analyses

The joinpoint analyses confirmed the increasing IS incidence trend among younger adults 18 to 44 years (Table 5). The APC was +1.3% (95% CI, 0.8-1.8) in men and +1.6% (95% CI, 1.0-2.3) in women. For those aged 45 to 64 years a decrease was observed during the first years but then increased briefly until 1996. After this, the rates declined by -0.4% (-0.7 to -0.1) in men and -0.6% (-1.0 to -0.2) in women. A similar decline at the beginning was observed among men and women aged 65 to 84 years but increased until 1998 for men and 1997 for women and decreased thereafter. In men the APC was -3.7% (-4.0 to -3.4) until 2010 with no detectable joinpoint, but in women, a slower decline of -2.5% (-2.9 to -2.1) was observed until 2005 and then changed to a more rapid decline with an APC of -5.1% (-5.8 to -4.4).

Twenty-year trends in long-term mortality risk in 17,149 survivors of ischemic stroke less than 55 years of age (Paper III).

The aim of this paper was to study the mortality risk in patients with a first time IS. A total of 17,149 men and women who survived for at least 28 days after hospitalization of IS were identified from 1987 to 2006. Of these, 4,520 (26.4%) were 18 to 44 years and 12,629 (73.6%) were 44 to 54 years old. During the study period 1,265 deaths occurred within 4 years in this study population.

Table 5. Age-standardized trends in the incidence of ischemic stroke among Swedish men and women from 1987 to 2010: Joinpoint analysis

Age group (years) and period	No of stroke Cases	Age-standardized rates per 10^5	Annual percentage change
Men	(min–max)*	(min–max)†	(95 % CI)
18–44 (y):			
1987–2010	125–189	7.5–11.4	1.3 (0.8–1.8)‡
45–64 (y):			
1987–1989	1362–1580	147–176	-8.7 (-12.8–-4.4)‡
1989–1996	1362–1872	147–175	2.6 (1.7–3.5)‡
1996–2008	1865–2032	165–177	-0.4 (-0.7–-0.1)‡
2008–2010	1878–2032	155–168	-3.2 (-7.4–1.2)
65–84 (y):			
1987–1989	6373–7075	1060–1190	-5.7 (-10.8–-0.2)‡
1989–1993	6943–7463	1277–1366	4.1 (1.3–7.0)‡
1993–1998	7434–7828	1240–1324	1.2 (-0.5–2.9)
1998–2010	5599–7828	819–1324	-3.7 (-4.0–-3.4)‡
Women	(min–max)*	(min–max)†	(95 % CI)
18–44 (y):			
1987–2010	81–176	5.1–10.8	1.6 (1.0–2.3)‡
45–64 (y):			
1987–1990	681–630	66–75	-3.7 (-7.9–0.5)
1990–1996	630– 963	66–91	6.4 (4.2–8.6)‡
1996–2010	962–1108	85–93	-0.6 (-1.0–-0.2)‡
65–84 (y):			
1987–1990	6851–6331	822–902	-2.9 (-4.6–-1.2)‡
1990–1993	6345–7357	822–956	5.5 (2.0–9.2)‡
1993–1997	7357–7633	956–1006	1.4 (-0.3–2.9)
1997–2005	7633–6063	827–1006	-2.5 (-2.9–-2.1)‡
2005–2010	6063–4983	638–827	-5.1 (-5.8–-4.4)‡

*The total number of cases in the age group for each particular year. †Comparison of mortality rates in each age group and time interval. ‡Annual percentage change is significantly different from zero at alpha = 0.05.

Mortality risk and survival after IS

For both men and women, the mortality risk compared to the general population was highest in the youngest age group (18-44 years). The risk of death was 9-fold higher (SMR=9.15, 95% CI=7.71–10.71) in men compared to the corresponding general male population with an AER of 1.31 per 100 person-years while women in the same age group had a 12-fold higher risk (SMR=12.12, 95% CI=9.60–14.94), with an AER of 0.93 per 100 person years. Corresponding SMRs in the older age group (45-54 years) were 5.11 (95% CI 4.75–5.49) in men and 6.37 (95% CI=5.68–7.10) in women, with AERs of 1.89 and 1.54 per 100 person-years, respectively (Table 6).

In men aged 18 to 54 years the 4-year mortality risk decreased by 32% (Hazard Ratio (HR) 0.68; 95% CI 0.56–0.82) and by 45% (HR 0.55, 95% CI 0.41–0.75) in women during the study period (Table 7). However, the SMRs for the last 5-year period (2002-2006) was still high in men (SMR=5.88, 95% CI 5.10–6.71) and women (SMR=5.91, 95% CI 4.68–7.29), with an AER of 1.60 and 0.97 per 100 person-years, respectively (Table 8).

Table 6. Four-year Standardized Mortality Ratio (SMR) in men and women with 95% Confidence Interval (CI) from 1987-2006

	Age group	Observed deaths (n)	Expected deaths (n)	SMR 95 % CI	AR*	AER†
Men	18–44 years	143	15	9.15 (7.71–10.71)	1.47	1.31
	45–54 years	735	143	5.11(4.75–5.49)	2.35	1.89
Women	18–44 years	79	6	12.12 (9.60–14.94)	1.01	0.93
	45–54 years	308	48	6.37 (5.68–7.10)	1.82	1.54
All	18–54 years	1265	155	8.15 (7.71–8.60)	1.92	1.69
Men	18–54 years	878	159	5.51 (5.15–5.88)	2.14	1.75
Women	18–54 years	387	54	7.06 (6.37–7.78)	1.57	1.34

*Absolute risk per 100 person-years. †Absolute excess risk per 100 person-years.

Table 7. Four-year mortality hazard ratios (95% CI) in men and women aged 18-54 years hospitalzed with a first IS from 1987-2006 by period

	Period	No of deaths	HR CI 95%†	Annual decrease, % CI 95%
Men	1987–1991	222	1.00 (ref.)	2.55% (1.38–3.71)
	1992–1996	224	0.74 (0.62-0.89)	
	1997–2001	229	0.69 (0.57-0.83)	
	2002–2006	203	0.68 (0.56-0.82)	
Women	1987–1991	83	1.00 (ref.)	3.33% (1.54–5.08)
	1992–1996	117	0.86 (0.65-1.15)	
	1997–2001	108	0.67 (0.50-0.89)	
	2002–2006	79	0.55 (0.41-0.75)	

†Adjusted for age and diabetes and interactions of age, diabetes and time.

Table 8. Four-years SMR in men and women aged 18-54 years with 95% CI by time period

	Period	Observed deaths (n)	Expected deaths (n)	SMR 95 % CI	AR*	AER†
Men	1987–1991	222	37	5.99 (5.23–6.81)	2.72	2.27
	1992–1996	224	43	5.13 (4.48–5.83)	2.10	1.69
	1997–2001	229	44	5.18 (4.53–5.87)	1.95	1.57
	2002–2006	203	34	5.88 (5.10–6.71)	1.93	1.60
Women	1987–1991	83	9	8.65 (6.89–10.61)	1.98	1.75
	1992–1996	117	14	7.90 (6.53–9.39)	1.82	1.59
	1997–2001	108	17	6.33 (5.19–7.58)	1.47	1.24
	2002–2006	79	13	5.91 (4.68–7.29)	1.17	0.97

*Absolute risk per 100 person-years. †Absolute excess risk per 100 person-years.

The overall 4-year survival after IS improved during the study period (Figure 8). For women there was a continued improvement over the four 5-year period but among men the survival rates for the third and the fourth period were nearly identical.

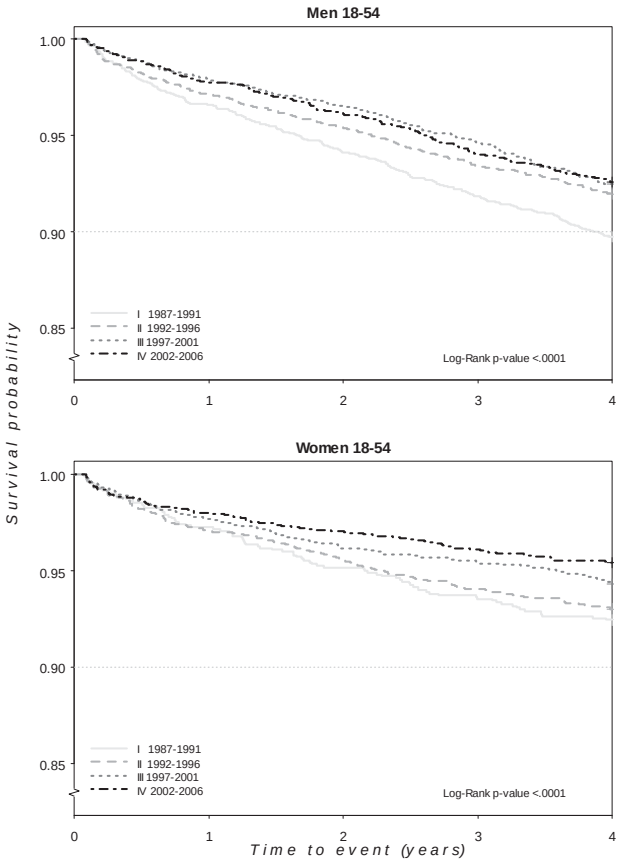

Figure 8. Four-year trend in survival probability by periods 1987–1991, 1992–1996, 1997–2001, 2002–2006 among men and women aged 18–54 year with a first ischemic stroke.

In men, half of all deaths after IS were related to CVD (50.3%), with a majority of all cases due to CHD (23.5%) and the rest from malignancies (15.3%) or other causes (34.4%). For women, less than 40% were due to CVD with more than half of all deaths related to malignancies (28.4%) and other causes (35.1%) (Figure 9).

Trends in risk of recurrence after first ischemic stroke among younger adults under 55 years of age in Sweden (Paper IV).

This paper investigates temporal trends in the risk of recurrent IS among survivors of IS. The same population as for Paper III was used in this study. A total of 2,432 IS patients (14.2%) out of 17,149 cases of IS suffered from a recurrent stroke within 4 years (1,579 men and 853 women). Hypertension was the most prevalent comorbidity diagnosis in both men (23.7%) and women (19.8%). Among men the prevalence in comobidities change over time for hypertension, congenital heart disease, AF, HF,

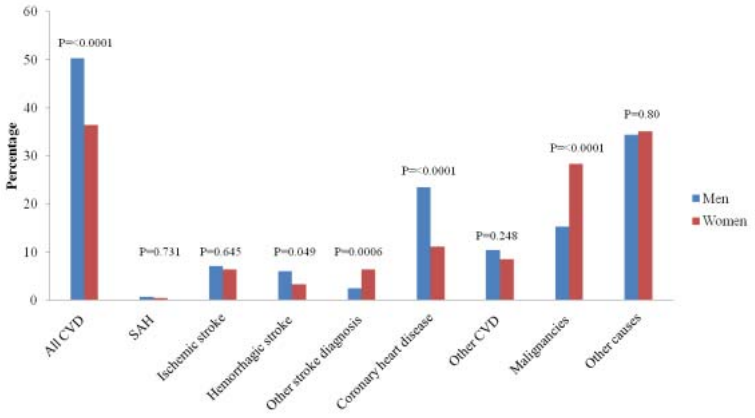

Figure 9. Cause of Death in Men and Women aged 18 to 54 year with a first ischemic stroke from 1987 to 2006

malignancy, chronic respiratory disease and IHD. Corresponding changes for women was hypertension, congenital heart disease and chronic respiratory disease ($p<0.001$). The prevalence of diabets did not change significantly during the study period for both men and women (Figure 10).

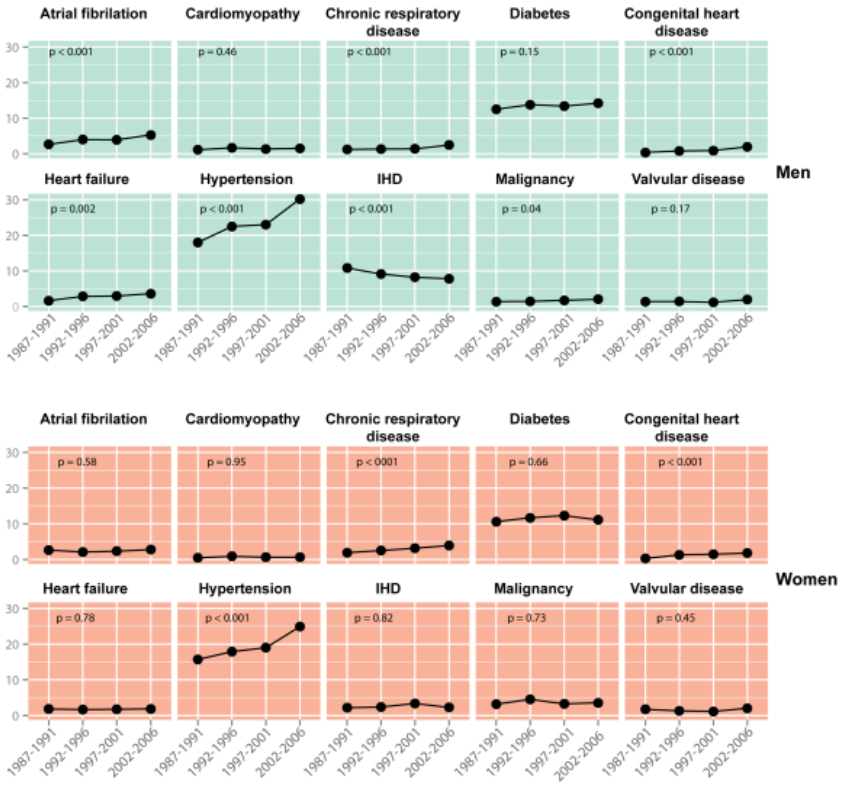

Figure 10. Trends in baseline comorbidites in men and women divided by period.

Temporal trends in risk of recurrent IS

From the first to the last period, the 4-year risk of recurrent IS decreased by 55% (HR 0.45, CI 0.39-0.53) in men and 59% (HR 0.41, 95% CI 0.33-0.50) in women with an average recurrence rate of 3.04 and 2.52 per 100 person-years, respectively (Table 9).

Table 9. Four-year hazard ratios for recurrent stroke in men and women

	Period	No at risk	No of events	Observation years	Incidence rate per 100 observation years	Age adjusted HR[†] (CI 95 %)
Men						
0-4 years	1987–1991	2163	473	6818	6.94	1.00 (ref.)
	1992–1996	2790	441	9444	4.67	0.69 (0.60-0.78)
	1997–2001	3047	367	10813	3.39	0.51 (0.44-0.58)
	2002–2006	2739	298	9813	3.04	0.45 (0.39-0.53)
Women						
0-4 years	1987–1991	1100	227	3505	6.48	1.00 (ref.)
	1992–1996	1678	255	5703	4.47	0.71 (0.59-0.85)
	1997–2001	1899	212	6725	3.15	0.51 (0.42-0.61)
	2002–2006	1733	159	6310	2.52	0.41 (0.33-0.50)

[†]Adjusted for age and interactions of age and time.

Regardless of time periods, the recurrence rate was highest within the first year (Table 10). At time interval 1 to 6 months the recurrence rate in men during the last period (2002-2006) was 8.03 per 100 person-years, 4.06 at 6 to 12 months, 1.85 at 1 to 2 years, 1.96 at 2 to 3 years and 1.99 at 3 to 4 years. Corresponding estimates for women were 6.03 at 1 to 6 months, 5.52 at 6 to 12 months, 1.77 at 1 to 2 years, 1.23 at 2 to 3 years, and 1.05 at 3 to 4 years. The risk of recurrent IS at time interval 1 to 6 months decreased by 64% (HR 0.36, 95% CI 0.28-0.45) in men from the first (1987-1991) to the last period, 58% (HR 0.42, 95% CI 0.30-0.59) at 6 to 12 months, and 58% (HR 0.42, 95% CI 0.29-0.61) at 1 to 2 years. However, there were no significantly improvements at 2 to 3 years (HR 0.77, 95% CI 0.51-1.17) or 3 to 4 years (HR 0.79, 95% CI 0.51 -1.21). Among women, the risk of recurrent IS decreased by 76% (HR 0.24, 95% CI 0.17-0.33) at 1 to 6 months, 41% (HR 0.59, 95% CI 0.37-0.94) at 6 to 12 months until the third period (1997-2001), however, this was not sustained through the final period (HR 0.77, 95% CI 0.49-1.20). There was a decrease of 56% (HR 0.44, 95% CI 0.27-0.72) at 1 to 2 years and of 55% (HR 0.45, 95% CI 0.23-0.89) until the third period at 2 to 3 years but again not sustained into the final period. No significant improvement was observed at 3 to 4 years (HR 0.99, 95% CI 0.42-2.31).

Table 10. Incidence rate and hazard ratio over time of recurrent IS in men and women divided by period

	Period	No. at risk	No. of Events*	Observation years	Incidence rate per 100 observation years	Age adjusted HR† (95% CI)
Men						
1-6 months	1987-1991	2163	230	1011	22.75	1.00 (ref)
	1992-1996	2790	221	1327	16.65	0.74 (0.61-0.89)
	1997-2001	3047	148	1478	10.01	0.45 (0.36-0.55)
	2002-2006	2739	107	1332	8.03	0.36 (0.28-0.45)
6-12 months	1987-1991	1889	88	914	9.63	1.00 (ref)
	1992-1996	2527	65	1237	5.25	0.55 (0.40-0.75)
	1997-2001	2865	58	1411	4.11	0.43 (0.31-0.59)
	2002-2006	2605	52	1282	4.06	0.42 (0.30-0.59)
1-2 years	1987-1991	1780	75	1717	4.37	1.00 (ref)
	1992-1996	2436	67	2385	2.81	0.64 (0.46-0.89)
	1997-2001	2785	62	2732	2.27	0.51 (0.37-0.72)
	2002-2006	2526	46	2489	1.85	0.42 (0.29-0.61)
2-3 years	1987-1991	1661	41	1623	2.53	1.00 (ref)
	1992-1996	2333	50	2287	2.19	0.85 (0.56-1.29)
	1997-2001	2688	52	2643	1.97	0.76 (0.50-1.14)
	2002-2006	2442	47	2400	1.96	0.77 (0.51-1.17)
3-4 years	1987-1991	1585	39	1553	2.51	1.00 (ref)
	1992-1996	2243	38	2208	1.72	0.68 (0.43-1.06)
	1997-2001	2595	47	2549	1.84	0.72 (0.47 -1.10)
	2002-2006	2350	46	2310	1.99	0.79 (0.51 -1.21)
Women						
1-6 months	1987-1991	1100	134	511	26.22	1.00 (ref)
	1992-1996	1678	140	797	17.57	0.69 (0.54 -0.87)
	1997-2001	1899	104	917	11.34	0.45 (0.35 -0.58)
	2002-2006	1733	51	846	6.03	0.24 (0.17-0.33)
6-12 months	1987-1991	950	33	462	7.14	1.00 (ref)
	1992-1996	1512	32	741	4.32	0.60 (0.37-0.98)
	1997-2001	1773	37	870	4.25	0.59 (0.37- 0.94)
	2002-2006	1661	45	815	5.52	0.77 (0.49-1.20)
1-2 years	1987-1991	905	35	878	3.99	1.00 (ref)
	1992-1996	1465	36	1437	2.50	0.62 (0.39-0.99)
	1997-2001	1721	41	1683	2.44	0.60 (0.38-0.94)
	2002-2006	1607	28	1580	1.77	0.44 (0.27-0.72)
2-3 years	1987-1991	853	17	840	2.02	1.00 (ref)
	1992-1996	1408	26	1383	1.88	0.89 (0.48-1.65)
	1997-2001	1655	16	1640	0.98	0.45 (0.23 – 0.89)
	2002-2006	1563	19	1550	1.23	0.57 (0.30 – 1.10)
3-4 years	1987-1991	824	8	815	0.98	1.00 (ref)
	1992-1996	1363	21	1346	1.56	1.51 (0.67-3.40)
	1997-2001	1627	14	1614	0.87	0.79 (0.33-1.90)
	2002-2006	1532	16	1519	1.05	0.99 (0.42-2.31)

†Adjusted for age and interactions of age and time. *Death from other causes is not presented.

The cumulative risk of recurrent IS during the last period (2002-2006) was 11.8% (95% CI 8.40-11.46) in men and 9.8% (95% CI 8.40-11.46) in women (Figure 11). From the first period (1987-1991) to the last period (2002-2006) stroke free survival improved by 70.2% (95% CI 68.25-72.11) to 83.0% (95% CI 81-56-84.38) in men and from 73.5% (95% CI 70.83-76.05) to 87.1% (95% CI 85.40-88.57) in women (Figure 12).

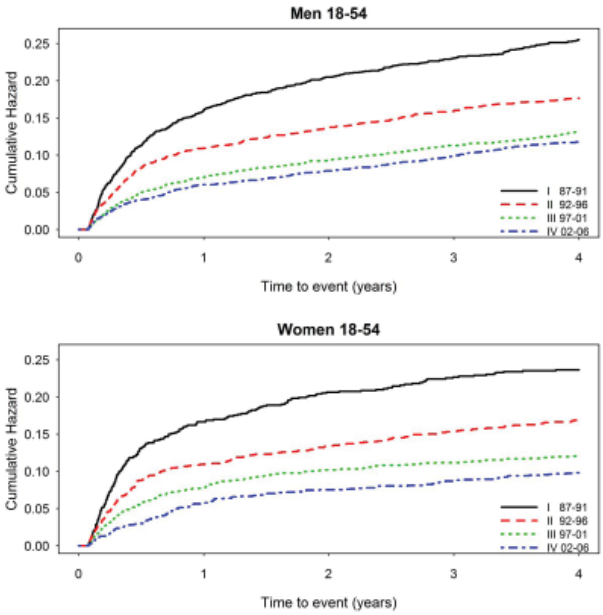

Figure 11. Cumulative risk of recurrent ischemic stroke in men and women 18 to 54 years divided by period.

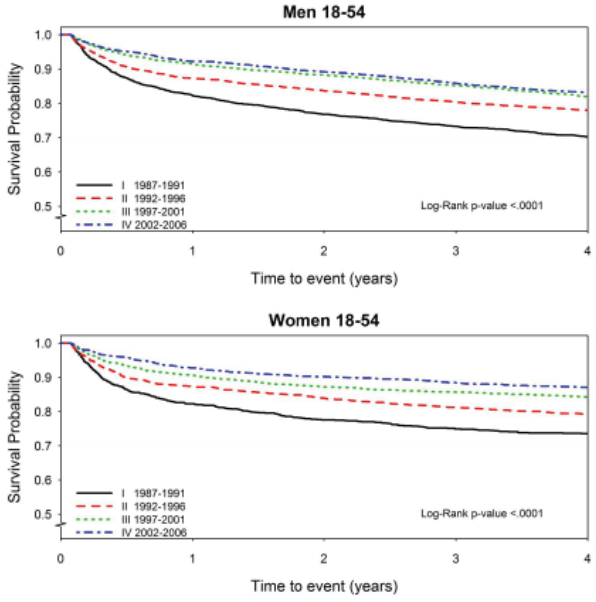

Figure 12. Stroke free survival in men and women 18 to 54 years divided by period.

DISCUSSION

Stroke in a middle-aged population (Paper I)

Stroke is a heterogeneous disease with various subtypes. Hemorrhagic stroke and ischemic stroke differ not only by their causes but also in having different risk factors.[11] The European SCORE model uses age, gender, SBP, serum cholesterol and smoking status to estimate the risk of a CVD over a 10-year period. However, the impact of these risk factors may differ over a long period of time and also separately for CHD and stroke. In Paper I we investigated to what extent the use of SBP, hypertension (including antihypertensive treatment), serum cholesterol and smoking status could be used to predict the short-term and long-term risk of CHD and stroke. For the individual risk factors we found that most of them were correlated to CHD and stroke but not all. High serum cholesterol levels did not increase the risk of stroke, confirming some previous studies on this subject which have failed to find any association between serum cholesterol and overall stroke risk.[22] However, some reports have found high serum cholesterol to increase the risk of IS while others have observed an inverse relationship between serum cholesterol and hemorrhagic stroke.[24, 26-28] For smoking status, we somewhat unexpectedly found that smoking at baseline did not increase the risk of stroke after adjusting for competing risk. This result should not be interpreted to mean that smoking has no effect on stroke risk. On the contrary, both passive and active smoking has previously been related to increased risk of stroke.[33] A possible explanation for our result could be due to premature deaths and a diminishing numbers of smokers over time. This may have contributed to an underestimation of the risk in our population. In Sweden, smoking rates have declined since the 1980s.[43] In Gothenburg the proportion of smokers among middle aged men decreased from 56% in 1970-1973 to 21.5% in 2003.[103] Similar development was found in the northern part of Sweden as well. For example, smoking prevalence declined from 19% in 1986 to 9% in 2004 among men.[104] The improvements are most likely attributed to better knowledge about the negative effects of cigarette smoking but also to several effective interventions against smoking such as increased price on tobacco, age limit, smoking restrictions in public places and ban on smoking advertisements.

For those men with adverse levels of risk factors at baseline we reported a high risk of developing CHD when compared to the low risk group after adjusting for age and competing risk but this was not reproduced for stroke. These results suggest that the sum of the risk factors used in the SCORE model differs for CHD and stroke over time. Therefore, it is our belief that stroke should be separated from the general concept of CVD when developing risk models for use in middle-aged population. Adding other major risk factors such as diabetes, obesity or sedentary lifestyle could be a more effective way to improve the short-term and long-term prediction of stroke.

Trends in stroke incidence over time (Paper II)

In a previous report on the Swedish IPR the incidence of stroke increased from 1989 to 2000 among people aged 30 to 65 years.[91] The STROMA study (stroke register in Malmö) found a similar trend but among people aged 50 to 79 years.[105] Similar

findings were also observed in the Lund-Orup study but with a leveling off of stroke incidences rates in 2001 to 2002.[106, 107] The Swedish National Institute of Public health (Swedish: Folkhälsomyndigheten) reported that the incidence rate of stroke has decreased in most age groups in the Swedish population since the mid 1990s but not among those 35 to 44 years old. Instead, the risk increased by 18% in men and 16% in women from 1995 to 2012.[43] We observed that the incidence rate for a first-time IS during the past 24-year period decreased among people aged 65 to 84 years, also starting in the mid 1990s. A similar but slower decrease was found among people 45 to 64 years old. In contrast, the incidence among younger adults increased by about 1.5% per year throughout the study period. Mortality rates from IS decreased in all age groups.

Over the past two decades there have been significant changes in CVD risk factors in Sweden that could potentially explain the recent trends in incidence and mortality.[108] For example, the Swedish IMPACT model showed that a majority of the decline in mortality rate in CHD were contributed to a decrease in cholesterol levels.[109] However, the relationship between overall stroke risk and cholesterol is still not clear but lower levels could be an indicator for other dietary changes in the population. Smoking rates in Sweden has decreased over the past 20 years which could also have contributed to a decline in stroke mortality. The prevalence of people with hypertension decreased from 1990 to 2010 as did the proportion of people using antihypertensive treatment.[110] In our population, the prevalence of hypertension increased but this was most likely due to changes in the definition of hypertension over time, but also in the incentives of registering more diagnoses with the Diagnosis related groups system introduced in Sweden in the 1990s. Improved primary prevention and better medical treatments may therefore have led to decreasing incidence trends of IS among older adults. The continuing increase of IS among younger adults is more difficult to explain. Since stroke is an uncommon disease in this age group few studies are available. One study found that even among younger stroke patients the burden of CVD risk factors was high.[111] Despite recent favorable development of some risk factors over time, obesity rates have increased in Sweden over the past years especially among younger and middle-aged people which may have had an adverse effect on other risk factors.[43, 103] This trend is most likely attributable to a combination of a more sedentary lifestyle and higher intake of unhealthy food. Smoking rates among younger persons have not changed for the past years in Sweden and, accordingly, are likely not the cause of the increased incidence of IS.[43] Further studies are needed to better understand the cause of this adverse trend in the young.

Prognosis after stroke (Paper III and IV)

The mortality risk after stroke is highest within the first year and varies between 4% to 5% among younger stroke patients but decreases thereafter to less than 2% in the subsequent years.[112-115] However, most of the previous studies were based on few cases and with a short follow-up time. Two separate studies, the Helsinki Young Stroke registry and the FUTURE study (The Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation) reported a 5-year cumulative mortality risk of 10.7% and 5.8%, respectively, rates which are not dissimilar to

our findings.[94, 116] However, our study adds that the mortality risk decreased by 32% in men and 45% in women. In addition, the FUTURE study reported a SMR of 3.9 whereas we observed a slightly higher SMR in the last period (2002-2006), 5.88 for men and 5.91 for women.

The risk of a recurrent stroke among younger adults with IS varies between 1.5% to 4% in the first year, and decreases thereafter to less than 3% yearly.[112, 114, 115, 117] Previous findings from the Helsinki Young Stroke registry and the FUTURE study reported a recurrent stroke risk of about 10% after 5 years.[118, 119] We found that the risk of recurrent IS declined by 55% in men and 59% in women. Most of the risk reduction occurred within the first months but the effect was largely sustained over the first 2 to 3 years after an IS. Similar trends in risk reduction have been observed in other studies as well but mostly among older patients.[120, 121] The 4-year cumulative risk of recurrent IS was 11.8% in men and 9.8% in women during the last period (2002-2006) in our study which is slightly higher than in the other studies.

Prognosis after stroke has improved over time and this trend is most likely a combination of better primary and secondary prevention. For example, better antihypertensive, antiplatelet and anticoagulation treatments are likely factors that probably have contributed to fewer recurrent events. Treatment with thrombolysis and prescription of secondary prevention medications has increased during the study period which may have contributed to less severe stroke cases and better outcome.[5, 122] However, Glader et al reported that persistent use of secondary preventive medications decreased within the first 2 years after IS, particularly for statins and warfarin.[123] This might partially explain why no significant improvements were observed for men and women at time interval 3 to 4 years in our study. In addition, over 90% of all stroke patients are now treated at a stroke unit in Sweden which is a significant improvement when compared to the 1990s.[5] However, despite these improvements almost 1 in 6 had either died or had a recurrent IS within 4-years. Younger patients are still at substantial risk of death and recurrent IS with increased risk of disability and long-lasting consequences, which emphasizes the importance of further research on this group of patients.

Strengths and limitations

Limitations in Paper I include relatively high levels of some of the risk factors in the PPS which could mean that these results might not be applicable in a more contemporary setting. This applies particularly to BP levels. Different methodologies when measuring the BP levels have been used for instance using the lowest level reading in a series or measuring in the morning as opposed to in the late afternoon as in our study but decreasing levels in the population have also been observed.[124] Cholesterol was high in our population but in comparison to other communities the mean value was lower than in other similar population at the time such as the Oslo and FINRISK populations.[125, 126] Smoking rates was also quite high when compared to the levels of today and accordingly the number of people in the optimal group was small (1.8% of the total population). Therefore, the low risk group was used as the reference group to provide a meaningful comparison when calculating the SHR. In addition, we used only single measurements for the risk factors and these may have changed during the

35-year follow-up time. Even so, and with these limitations in mind, single measurement of these main risk factors in midlife was quite predictive for events occurring decades after the baseline investigation.

Stroke is an uncommon disease among younger adults; large populations are often needed to identify a sufficient amount of younger patients. A major strength in Paper II to IV is therefore the use of the Swedish IPR which has a near complete national coverage of all hospitalized stroke cases for an extended period of time. All patients with a first time IS that occurred for the past two decades are included. This reflects national trends in incidence of IS and prognosis after a stroke. Among the limitations are the uncertainties of diagnosis from earlier data and in the varying judgments on the validation of stroke cases with one study showing up to one third false-positive diagnosis.[96, 127] Since a proportion of these were most likely former stroke cases that has been classified as new stroke events and study II represents incident cases differences in recurrent stroke is unlikely to explain the large reduction among the old. No other clinical data such as diagnosis in the primary health care, imaging results, functional loss or recovery of function are available. However, imaging diagnostics have been routinely used throughout the study period which reliably excludes hemorrhagic strokes and cerebral malignancies. In addition, there are no specific diagnose codes for recurrent IS in the IPR. To avoid false-positive cases in study IV we used a strict protocol and selected only those that occurred after 28 days, specifying a time window of at least 2 days after discharge.

CONCLUSION

- The prediction of CHD and stroke in middle-aged men differs substantially over time when using the conventional risk factors from the SCORE model. Our findings indicated that the use of these risk factors can effectively predict the short and long-term risk of CHD but not stroke to the same extent.

- The incidence of IS among elderly people in whom most cases occurs peaked during the 1990s but are now decreasing whereas the decline in middle-aged people is less steep. In contrast, the incidence of IS among younger is now increasing.

- The mortality risk among younger IS patients have decreased in both men and women for the past two decades but despite this the risk of death was nearly 6-fold higher when compared to the same age-group in the general population.

- The risk of recurrent IS has decreased over time particularly during the first year after IS. Improvements in recurrence are most likely due to better secondary prevention and treatment of stroke patients over time. However, even with these improvements in mind nearly 1 in 6 younger patients had either died or suffered from a recurrent event within 4 years.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Stroke är en av de vanligaste orsakerna till förtidig död och handikapp hos vuxna runt om i världen. I Sverige drabbas årligen ca 30,000 personer av en förstagångsstroke varav 23,000 är förstagångsfall. Sjukdomen medför många gånger en stor förändring i det dagliga livet och en påverkan på individens livskvalitet. Det övergripande syftet med avhandlingen var att studera vilka riskfaktorer som kan användas för att förutspå både korttids- och långtidsrisk för hjärtinfarkt och stroke, undersöka trender i förekomsten av ischemisk stroke (IS) i olika åldersgrupper samt prognos efter sjukdom hos yngre vuxna (<55 år). I delstudie I har en göteborgsbaserad kohort (Primärpreventiva studien - PPS) använts. Information från Patientregistret och Dödsorsaksregistret har använts i delstudie I till III.

Den europeiska SCORE-modellen skapades för att prediktera den 10-åriga risken att dö av en kardiovaskulär sjukdom bland medelålders personer. Modellen använder sig av fem riskfaktorer: ålder, kön, blodtryck, kolesterol och rökning för att prediktera risk. I den första studien fann vi att både korttids- och långtidsrisken att insjukna i hjärtinfarkt eller stroke skiljer sig avsevärt åt för dessa riskfaktorer. Detta beror troligtvis på att effekten av de individuella riskfaktorerna skiljer sig åt mellan hjärtinfarkt och stroke över tid, men också långtidsrisken kan påverkas av risken att dö i förtid av andra orsaker – ”competing risk”.

Under perioden 1987 till 2010 minskade insjuknandet av IS för äldre (≥65 år) och medelålders personer (45-64 år). Insjuknandet för yngre vuxna (18-44 år) har istället ökat med ca 1.5% årligen under samma period. Det är inte helt klarlagt vad som har orsakat den stora minskningen hos äldre personer men förändringar i riskfaktorer över tid och bättre förebyggande behandling är troliga orsaker. Varför insjuknandet ökar hos yngre vuxna är en komplex och svår fråga att svara på. Till viss del beror ökningen möjligen på bättre rapportering till följd av bättre diagnostik, dock syns detta inte ha påverkat de äldre åldersgrupperna. En annan orsak skulle kunna vara den ökade fetmatrenden i Sverige vilket skulle kunna ha påverkat andra riskfaktorer under samma period.

Prognosen efter sjukdom för yngre patienter (18-54 år) med IS har förbättrats under perioden 1987 till 2006. Den 4-åriga risken för död efter IS minskade över tid hos både män och kvinnor. En liknande utveckling observerades även för risken att drabbas av återinsjuknande. Den största förbättringen skedde under de första 6 månaderna. Troliga orsaker till förbättrad prognos är bättre sekundärprevention och införandet av specialiserade strokekliniker i Sverige under de senaste 20 åren.

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