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Aked, Joseph

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+46 46-222 00 00

Stroke Epidemiology and Outcome in Southern Sweden

JOSEPH AKED
DEPARTMENT OF CLINICAL SCIENCES LUND, NEUROLOGY | LUND UNIVERSITY

Stroke Epidemiology and Outcome in Southern Sweden

Joseph Aked, MD

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Faculty opponent
Clinical Associate Professor Thomas Clement Truelsen, Department of Clinical Medicine, Copenhagen University Hospital, Rigshospitalet, Denmark

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Abstract

Background: Stroke is a common cause of mortality and disability worldwide and continuously updated, thorough information of its occurrence and outcome is needed. In recent years, multiple advances have been made in stroke prevention and treatment that may have changed the epidemiology and outcome of stroke.

Aims: To investigate updated population-based stroke epidemiology as well as long-term survival, recurrence and functional outcome in southern Sweden.

Methods: Paper I: A population-based cohort of 413 consecutive patients with first-ever stroke in 2015-2016 was assembled using the prospective hospital-based stroke studies Lund Stroke Register (LSR) and Riksstroke, as well as retrospective searches of primary care, outpatient clinic and autopsy sources. Age- and sex-standardized incidence rates were calculated and compared with a prior study from the same study area in 2001-2002.

Paper II: A subset of the population-based cohort of 400 patients (only ischemic stroke and intracerebral hemorrhage) was compared with LSR and Riksstroke regarding case ascertainment and which patients were not included in the hospital-based stroke studies. Paper III: The 400 individuals in the population-based cohort were followed up after 3 years regarding survival and causes of death by using the Swedish Causes of Death Register, and stroke recurrence by using medical record review. Index and recurrent strokes were classified by pathogenetic mechanism using the TOAST classification. Stroke survival at 3 years was compared with prior studies in our area from 1983-1985, 1993-1995, and 2001-2002.

Paper IV: The population-based cohort was followed-up in-person or via telephone at 3-4 years regarding functional outcome (mRS), dependency in activities of daily living (ADL), and health-related quality of life (HRQoL). Data were also collected on potentially correlated health problems after stroke such as fatigue, cognitive impairment and depression.

Results: Paper I: The total population-based age- and sex-standardized rate of stroke incidence was 165 per 100 000 person years in our study area, a 33% decrease compared with a population-based study in our area from 2001-2002. However, stroke incidence rates did not change for hemorrhagic stroke or among those <65 years.

Paper II: LSR detected 363 (91%) of cases while Riksstroke detected 328 (82%). Patients undetected by the hospital-based studies had high case fatality (44% vs 9%; p=0.001), and those only detected in primary care (n=11) often lived in nursing homes (57%). Those not detected by Riksstroke had less severe stroke (median NIHSS 3 vs 5; p=0.013).

Paper III: In total, 265 (66%) survived 3 years after first-ever stroke. Among individuals with ischemic stroke, cardio-aortic embolism as pathogenetic mechanism was associated with the lowest 3-year survival (51/91; 56%). Cardiovascular disease was the cause of death in 59% of cases (79/135). Meanwhile, 8% (32/400) had a recurrent stroke within 3 years, and the pathogenetic mechanism of ischemic stroke changed between first-ever stroke and recurrence in 16/29 (55%) cases. Three-year survival improved between the 1980s and the present study (56% vs 66%; p=0.002), but survival did not change significantly between the early 2000s and the present study (64% vs 66%; p=0.48. Paper IV: In all, 202 individuals were clinically followed-up after a median of 3.2 years, while 47 (12%) stroke survivors were lost to follow-up. Among followed-up survivors, 147 (73%) had favorable functional outcome (mRS≤2) and 134 (69%) reported good-excellent HRQoL. Age, stroke severity, professional care pre-stroke and recurrent stroke (all p<0.001) were predictors of poor functional outcome. Among follow-up variables, fatigue (p=0.001), and stroke severity (p<0.001) were associated with dependency in ADL, and fatigue (p<0.001) was also associated with worse HRQoL.

Conclusions: Stroke incidence and survival have improved over recent decades, however some subgroups of stroke have not improved in the same manner. Thorough population-based epidemiological studies of stroke are important to avoid and to possible selection bias in hospital-based stroke studies. Around 3 of 10 long-term stroke survivors have poor outcome, and fatigue may be a significant contributor to post-stroke function and health.

Key words stroke, epidemiology, incidence, survival, recurrent stroke, outcome, functional outcome, health-related quality of life

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Joseph Aked, MD

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List of papers

This thesis is based on the following four papers, henceforth referred to in the text by their Roman numerals as below. The papers are appended at the end of the thesis with due permission from the publishers.

I. Aked J, Delavaran H, Norrving B, Lindgren A. Temporal Trends of Stroke Epidemiology in Southern Sweden: A Population-Based Study on Stroke Incidence and Early Case-Fatality. *Neuroepidemiology.* 2018;50:174-182.

II. Aked J, Delavaran H, Norrving B, Lindgren A. Completeness of case ascertainment in Swedish hospital-based stroke registers. *Acta Neurologica Scandinavica*, 2019;141:148-155.

III. Aked J, Delavaran H, Lindgren A. Survival, causes of death and recurrence up to 3 years after stroke: A population-based study. *European Journal of Neurology*. (2021). Ahead of print. DOI:10.1111/ene.15041.

IV. Aked J, Delavaran H, Wennerström F, Stenman M, Jensen M, Lindgren A. Functional Status and Health-Related Quality of Life at Three to Four Years After First-Ever Stroke: A Population-Based Study. Unpublished manuscript.

Abbreviations

ADL	activities of daily living
BI	Barthel Index
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CCS	Causative Classification System for Ischemic Stroke
CE	cardio-aortic embolism
CI	confidence interval
CT	computed tomography
DALY	disability-adjusted life year
DOAC	direct oral anticoagulant
EQ-5D	European Quality of Life-5 Dimensions
FAS	Fatigue Assessment Scale
GBD	Global Burden of Disease
HR	hazard ratio
HRQoL	health-related quality of life
ICD-10	International Statistical Classification of Diseases and Health
ICF	International Classification of Functioning, Disability and Health Related Problems, tenth revision
ICH	intracerebral hemorrhage
IS	ischemic stroke
IQR	interquartile range
LAA	large-artery atherosclerosis
LSR	Lund Stroke Register
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale

NPR	Swedish National Patient Register
OAC	oral anticoagulant
OCSP	Oxfordshire Community Stroke Project
PHQ-9	Patient Health Questionnaire
PROM	patient-reported outcome measure
PSCI	post-stroke cognitive impairment
PSD	post-stroke depression
PSF	post-stroke fatigue
SAH	subarachnoid hemorrhage
SAO	small-artery occlusion
SF-36	Short Form 36 Health Survey
SIS	Stroke Impact Scale
TIA	transient ischemic attack
TOAST	Trial of ORG 10172 in acute stroke treatment
UND	undetermined stroke subtype
UND-IS	undetermined pathogenetic mechanism of ischemic stroke
WHO	World Health Organization

Introduction

Stroke is the second most common cause of death and a leading cause of acquired disability worldwide [1-3]. The global burden of stroke has been projected to increase over coming decades [1, 4], despite recent major advancements in stroke prevention and acute stroke therapy [5, 6].

Consequent to recent therapeutic advancements as well as changes in the composition of the general population, the epidemiology of stroke is changing [7]. Detailed study of stroke epidemiology is imperative to understanding causes of stroke, real-life effects of treatment implementation, and to identify areas in need of address through additional research or policies to further reduce the burden of stroke.

A stroke can entail a considerable amount of functional loss, directly via neurological dysfunction, or via consequences such as depression, cognitive impairment and fatigue [8-11]. For stroke survivors, there is a great need to understand the prevalent mechanisms of this loss of function to be able to accurately prognosticate as well as establish future treatment targets to improve life after stroke.

This thesis aims to contribute to reducing the future burden of stroke by in-depth study of stroke epidemiology and outcome, thus identifying new insights into in which population groups stroke can be prevented, and which consequences can be best ameliorated to improve outcomes.

Stroke – Definitions and Terminology

The most widely used definition of stroke is based on the criteria proposed by the World Health Organization (WHO) stroke register in the 1970s: “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin” [12].

This definition provides a time-based clinical diagnosis that differentiates stroke from transient ischemic attack (TIA), which is classically defined as “episodes of temporary and focal cerebral dysfunction of vascular origin, which are variable in

duration, commonly lasting from 2 to 15 minutes, but occasionally lasting as long as a day (24 hours)" [13]. Furthermore, for an event to be classified as a stroke by the WHO definition, there should be no other apparent cause other than vascular, which eliminates events such as traumatic brain hemorrhages, epileptic episodes and migraine disorders from the definition. Vascular causes include cerebral infarction due to ischemia (ischemic stroke, IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). Finally, the addition of "at times global" also permits the inclusion of vascular neurological events that lead to coma, and subarachnoid hemorrhage without focal neurological symptoms [13, 14].

However, since the advent of more readily available and advanced neuroimaging techniques, it has been emphasized that radiological signs of cerebral infarction can be present among those with clinical TIAs, as well as that clinical stroke with symptoms lasting over 24 hours can be present without a cerebral lesion that can be visualized upon neuroimaging [15]. Therefore, the Stroke Council of the American Heart Association/American Stroke Association has suggested an updated "tissue-based" definition of stroke which includes any objective evidence of permanent central nervous system injury due to a vascular cause based on pathological methods or imaging – with or without clinical symptoms [15]. A major difference is that this also encompasses "silent" or "covert" cerebral infarction, i.e. lesions visible on neuroimaging that have not been associated with clearly defined neurological symptoms. A similar definition of stroke is also planned in the upcoming 11th revision of the International Classification of Diseases (ICD-11) [16]. In epidemiological and clinical research settings, the original WHO definition has nonetheless still been frequently used in recent years, and the current thesis uses the WHO definition of stroke.

Stroke is a heterogenous disease with many known causes, but the main types of stroke are IS, ICH and SAH. A recent global estimate gives that approximately 65% of incident strokes are due to IS, 26% due to ICH and 9% due to SAH [17].

Stroke Epidemiology

Global Burden of Stroke

Over the last decades, the Global Burden of Disease (GBD) study has registered a global shift in overall disease burden from communicable, maternal, neonatal and nutritional causes to non-communicable diseases [18]. This shift has mostly been driven by cerebro- and cardiovascular disease, including stroke [18]. Stroke was the second most common cause of death and disability-adjusted life years (DALYs) globally in 2016, causing 5.5 million deaths and 116 million DALYs [18].

The absolute number of global stroke cases has previously been projected to increase throughout the early 2000s primarily due to population growth and an ageing population [19], and a more recent European study has projected a 27% increase in the number of people living with stroke in the EU until the mid-2000s, while deaths and DALYs due to stroke are projected to decline [4]. European projections of developments in stroke epidemiology until 2047 are presented in Figure 1.

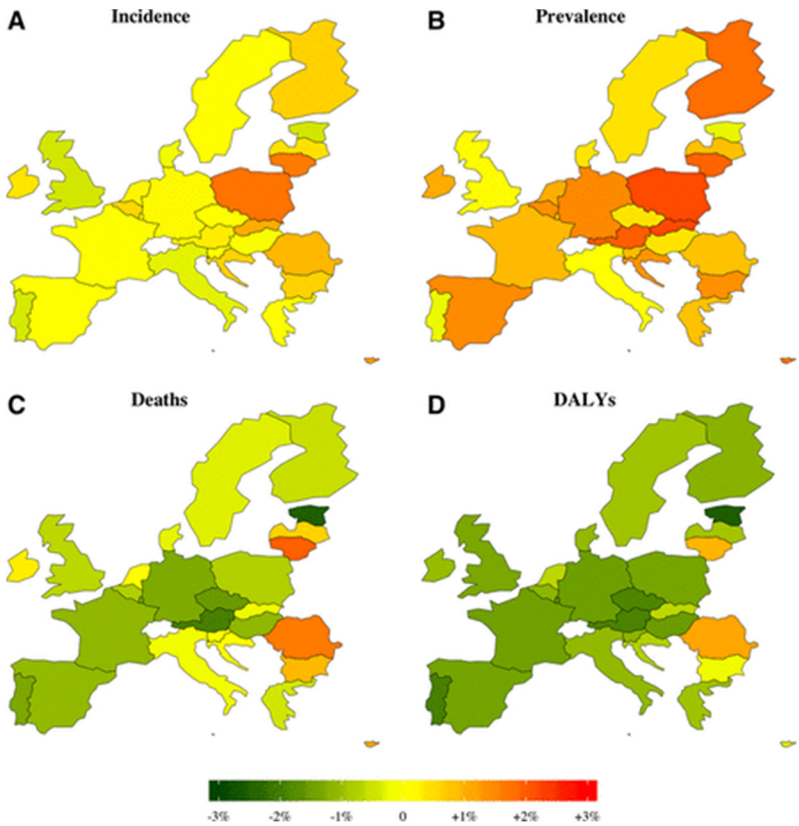

Figure 1. Projected average annual percentage change in crude rates of incidence, prevalence, death and disability-adjusted life years (DALYs) from 2018-2047. *Reprinted from Stroke, Vol. 51, Wafa et al., Burden of Stroke in Europe: Thirty-Year Projections of Incidence, Prevalence, Deaths and Disability-Adjusted Life Years, pp. 2418-2427, Copyright (2020), with permission from Wolters Kluver.*

The epidemiology and burden of stroke also has a substantial degree of geographical variation, wherein the burden of stroke is highest in Eastern Europe, North Asia, Central Africa and the South Pacific – and the difference between the most and least affected countries is approximately tenfold [20]. An important predictor of regional stroke burden is national income per capita, and global stroke epidemiology studies

therefore often differentiate between high-income and low- and middle-income countries [20].

Incidence and Time Trends

In high-income countries, stroke incidence rates have declined since the beginning of the 21st century, while simultaneously increasing in low- and middle-income countries [7, 21]. This decline appears to be mainly driven by a decrease in stroke incidence among those over 75 years [22], while certain studies have reported increasing stroke incidence among the young [23, 24]. A combination of incidence trends from several recently updated population-based studies reported in a 2020 systematic review is presented in Figure 2.

Suggested reasons for the recent decline in stroke incidence in high-income countries, despite an ageing population, include improved treatment of hypertension, atrial fibrillation, and diabetes, as well as decreased smoking prevalence [25, 26].

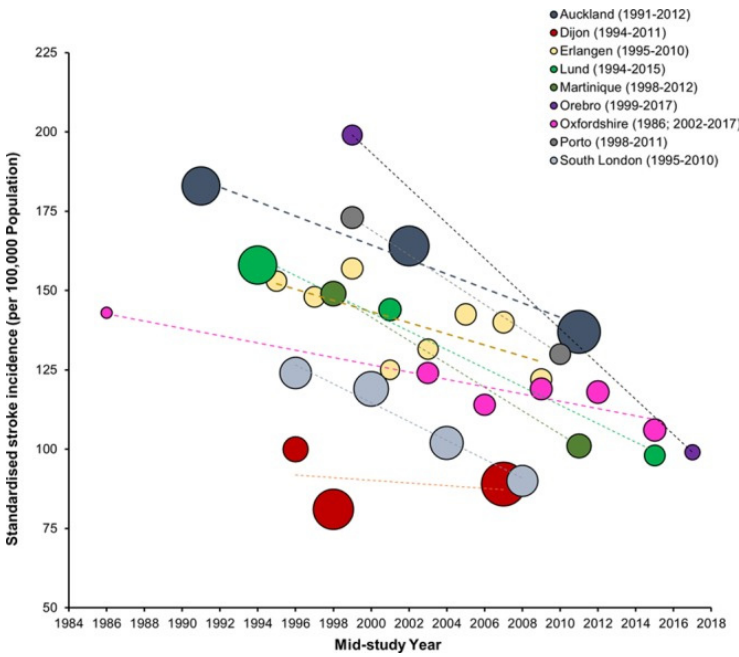

Figure 2. Temporal trends of standardized stroke incidence in population-based studies that reported data after year 2010. Reprinted from Stroke, Vol. 51, Li et al., Trends in Stroke Incidence in High-Income Countries in the 21st Century: Population-Based Study and Systematic Review, pp 1372-1380 Copyright (2020), with permission from Wolters Kluver.

Trends in Case-Fatality and Long-Term Mortality

Early case-fatality after stroke (death within 21-30 days) declined in high-income countries over several decades to between 17-30% in the 2000s, compared to 29-49% in the 1970s [21]. Long-term mortality has also declined in high-income regions [27], which has similarly been suggested to be due to better risk factor management, as well as improved acute stroke therapies [28, 29]. However, in certain regions, survival rates appear to be stagnating or worsening since the 2010s [30].

Prior population-based studies have shown that two thirds of individuals with nonfatal stroke subsequently die from vascular disease, and that nonfatal stroke is associated with a 5 times higher risk of death within one year compared to the general population [31]. Relative to the general population, stroke patients also have been reported to have excess mortality from cancer, accidents and suicide [31].

Epidemiological Methods in Stroke Studies

To be able to learn more about stroke through epidemiological studies, it is important that studies from around the world conform to similar standards for definitions, methods and data presentation. This allows comparisons between different geographical area and facilitates large-scale meta-analyses.

A set of criteria for optimal stroke epidemiology were first proposed by Sudlow and Warlow in the 1990s [32] and have since been updated in the 21st century, including recent adjustments for the new proposed clinical and tissue-based stroke definition [33, 34]. Among other criteria, these propositions include using a large, well-defined and stable population with a reliable method of estimating the amount of people in the population. Furthermore, population-based case ascertainment is recommended [33, 34]. Population-based case ascertainment means attempting to detect and register all stroke in the population, and not only registering stroke that is treated in a hospital for instance. Therefore, the proposed criteria recommend multiple overlapping sources of information of potential stroke cases, including data from hospitals, outpatient clinics, general practitioners' databases and death certificates [33, 34]. Ideally, an optimal stroke incidence study should be partly prospective and actively try to find new stroke cases, which is called "hot pursuit" in contrast to "cold pursuit" which refers to retrospective searching of data sources [33, 34].

In the last decades, several hospital-based stroke registers have been established, offering a valuable complement to time-consuming and more expensive population-based studies [35]. These hospital-based stroke registers often have the primary goal of monitoring and improving local quality of care – but have increasingly also been used to provide epidemiological estimates [35]. However, these registers can be at risk of selection bias due to not detecting certain types of stroke cases [36, 37].

Societal Costs of Stroke

Aside from the death and disability of individuals caused by stroke worldwide, stroke also has significant societal and economic costs. The economic costs derive from professional healthcare and social care costs, informal care from friends or family, as well as loss of work ability [38]. In 2017, the total cost of stroke across 32 European countries was estimated at 60 billion euros [38].

Calculations from the UK estimate that a new stroke costs an average of approximately 45 000 pounds (GBP) in the first year after stroke, and approximately 25 000 GBP in subsequent years [38].

In summary, stroke incidence and mortality have been declining over time, but the overall burden of stroke is still projected to increase – leading to substantial individual and societal harm. Therefore, it is important to assess if there are subgroups of stroke that have not been affected by recent developments in stroke epidemiology that may require increased focus.

Pathobiology

Ischemic Stroke

Ischemic stroke is caused by an acute occlusion of a brain artery, which impairs blood flow [39, 40]. A total obstruction of blood flow leads to death of brain tissue within 4-10 minutes, whereas blood flow <16-18 ml/100 g tissue per minute causes infarction within approximately an hour [39]. If blood flow is restored to the cerebral tissue prior to significant infarction, symptoms may only be transient – i.e. a TIA [39].

Cerebral infarction occurs partly through a necrotic pathway where brain cell cytoskeletons rapidly break down leading to cell death due to the energy failure induced by the lack of delivery of vital substrates such as oxygen and glucose [39]. Another mechanism of infarction is via apoptosis, wherein brain cells become programmed to die which can occur days to weeks later [38, 40]. When brain cells are deprived of oxygen and glucose, cell mitochondria fail to produce ATP [39, 40]. This leads to cell membrane ion pump dysfunction and cell depolarization which in turn causes higher levels of intracellular calcium and release of glutamate [39, 40]. Extracellular glutamate causes further neurotoxicity and free radicals produced by membrane lipid degradation and mitochondrial dysfunction cause catalytic destruction of cell membranes [39, 40]. A schematic flow-chart of the cascade of cellular injury in stroke is shown in Figure 3.

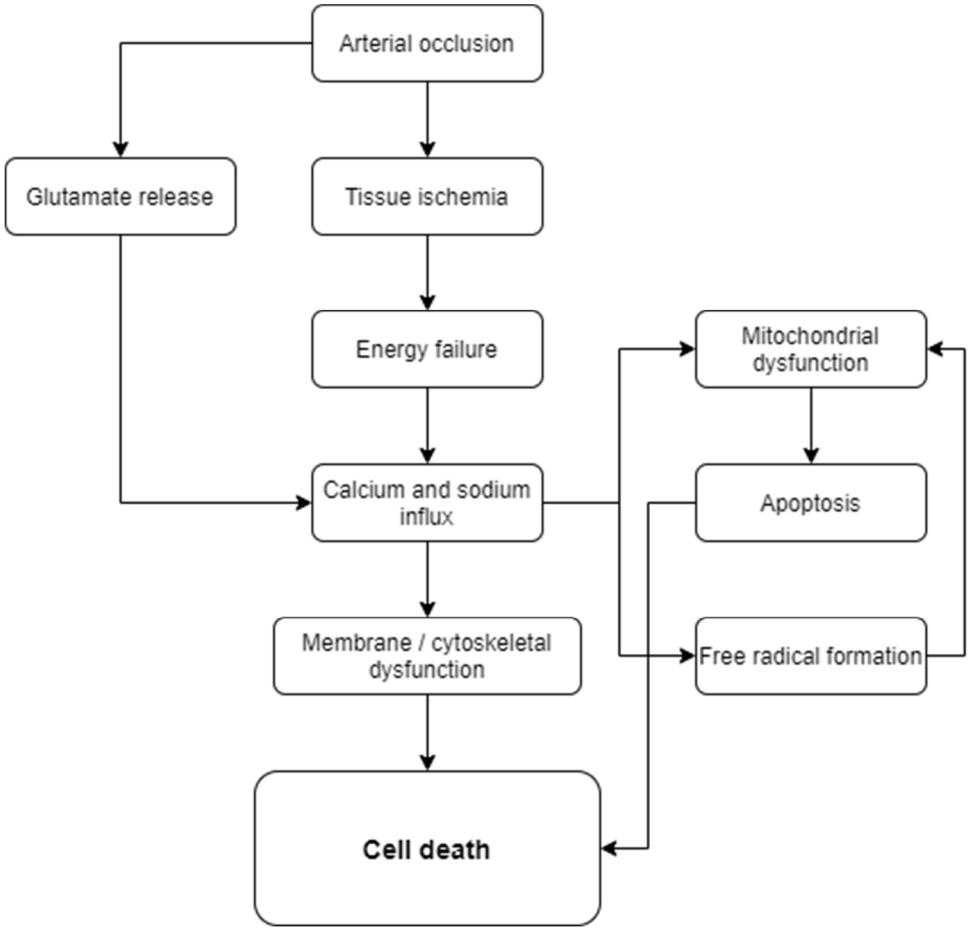

Figure 3. Schematic flow-chart of the cascade of cellular injury in acute ischemic stroke.

Cell damage is heterogenous in the affected area of the brain, and permanent damage develops within minutes in the center, or core, of the ischemic territory [40]. Between this area and adjacent areas of unaffected brain tissue lies the penumbra [40]. This area has lessened blood flow but not total energy failure initially [40]. Over time this area can progress to infarction due to excitotoxicity via glutamate release, inflammation due to adjacent ischemia, or apoptosis [40]. However, the penumbra area can potentially be salvaged upon rapid reperfusion, either spontaneously or via acute reperfusion therapy [40].

Hemorrhagic Stroke

According to a recent global estimate [17], 35% of stroke globally is hemorrhagic, i.e. due to bleeding in the brain tissue or in the meninges surrounding the brain. Hemorrhagic stroke is divided into intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), where ICH is approximately twice as common [17].

ICH, bleeding within the brain parenchyma, begins with the rupture of an intracerebral vessel and induces primary brain injury and cell death via mechanical compression which may in turn affect blood flow [41]. Further damage occurs via inflammatory cascades, oxidative stress and direct cytotoxicity of red blood cell components [41].

SAH is bleeding into the subarachnoid space, the area between the brains two innermost meninges, the arachnoid and pia mater [42]. SAH occurs due to cerebral aneurysm rupture in approximately 85% of cases and can subsequently cause brain injury via intracranial hypertension leading to hypoperfusion and cell apoptosis, hydrocephalus, cerebral edema and vasospasm [42].

A visual representation of the main pathological types of stroke is presented in Figure 4.

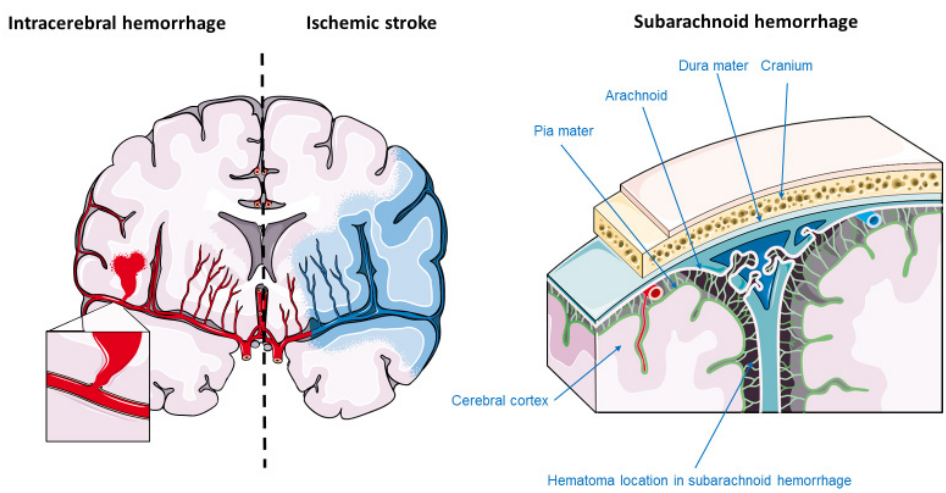

Figure 4. Visual representation of the main types of stroke. Images modified from smart.servier.com. Licensed under a Creative Commons Attribution 3.0 Unported License.

Pathogenetic Mechanisms of Ischemic Stroke

The most common method of classifying pathogenetic mechanisms of ischemic stroke is using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification [43], which classifies ischemic stroke into the following categories:

1. Cardio-aortic embolism
2. Large artery atherosclerosis
3. Small artery occlusion
4. Other causes
5. Undetermined cause

A similar classification adding a computerized algorithm, Causative Classification System for Ischemic Stroke (CCS) [44] has also been proposed, but the current ubiquity of the TOAST classification in stroke research makes comparisons between studies easier when using TOAST.

Cardio-Aortic Embolism

Cardio-aortic embolism (CE) is the most prevalent subtype of ischemic stroke, accounting for roughly 25-30% of ischemic stroke in European countries [27, 45]. However, there is a significant geographical variation and in Chinese populations, CE is the least common among the main TOAST classifications [46]. CE indicates a stroke caused by a blood clot formed in the heart, ascending aorta or aortic arch that travels through the arterial circulatory system and occludes a brain artery. The most common cause of CE is atrial fibrillation, a highly prevalent cardiac arrythmia that predisposes thrombus formation in the left atrium of the heart [47]. Other causes of cardio-aortic embolism include: systolic heart failure ; recent myocardial infarction; aortic arch atheroma; patent foramen ovale (PFO), which is a prevalent but weak stroke risk factor that can allow paradoxical emboli when blood clots from the venous circulation access the arterial circulation through the PFO [47]; infective endocarditis; and prosthetic heart valves [47-50]. CE is associated with the most severe stroke symptoms and highest case fatality among ischemic stroke mechanisms, and typically causes cortical lesions in multiple cerebrovascular territories [47].

Large Artery Atherosclerosis

Extra- and intracranial large artery atherosclerosis (LAA) is another major ischemic stroke subtype, responsible for approximately 10-15% of ischemic stroke in Western populations [27, 51], whereas in other areas of the world, LAA is a dominant pathogenetic mechanism of stroke [52]. Atherosclerotic plaques in arteries to the brain can cause stroke via artery-artery embolism from thrombus formation on the plaques; hypoperfusion because of narrowing of the artery lumen;

or branch atheromatous disease that causes occlusion of a penetrating artery due to plaques in a larger parent artery [52-54]. LAA typically causes territorial cortico-subcortical infarcts distal to a singular stenotic vessel, sometimes subcortical infarcts at the site of perforating arteries; or infarcts in border-zones between arterial territories [52].

Small Artery Occlusion

Small artery occlusion (SAO) is a major ischemic stroke subtype that constitutes around 25% of ischemic stroke [27] in Western countries. SAO is a part of the umbrella term cerebral small vessel disease that describes an array of pathological processes present in small arterioles in the brain [55]. Stroke due to cerebral small vessel disease is usually referred to as lacunar stroke with regard to its pathologic appearance, typically as a rounded lesion less than 15 or 20 mm in diameter in the territory of a single perforating artery [55, 56].

Other Causes

Other specific causes of ischemic stroke that are less common than the abovementioned major pathogenetic mechanisms include arterial dissection, fibromuscular dysplasia, hypercoagulable states, hematologic disorders such as stroke due to cerebral venous sinus thrombosis, sickle cell anemia, migraine-associated stroke, vasculitis, and hereditary small vessel diseases [57]. In the updated definition of stroke, infarction or hemorrhage in the central nervous system due to the thrombosis of a cerebral venous structure is necessary to fit the definition of stroke, whereas symptoms due to reversible edema do not qualify as stroke [15]. This group of pathogenetic mechanisms together account for about 3% of ischemic stroke [27].

Undetermined Causes

In roughly 35% of cases, no singular pathogenetic mechanism of ischemic stroke can be identified [27]. This can either be due to that two or more causes have been identified and are equally probable pathogenetic mechanisms; because thorough evaluation has been performed and not identified an identifiable pathogenetic mechanism; or because the evaluation after stroke was inadequate [57]. Cases where thorough investigation does not yield a possible pathogenetic mechanism are commonly referred to as cryptogenic stroke [58].

Causes of Intracerebral Hemorrhage

Spontaneous ICH (i.e. not due to trauma, bleeding from a cerebral tumor or iatrogenic causes) is commonly divided into the two main causes: hypertension-related ICH and ICH due to cerebral amyloid angiopathy (CAA) [59]. Hypertension-associated ICH's are typically located in the deep brain tissue, in proximity of deeply located branches from the main cerebral arteries (anterior,

medial or posterior cerebral artery, or basal artery) [60]. Meanwhile, ICH due to CAA is typically associated with bleeding in the cortex or subcortical white matter, a.k.a. lobar ICH [61]. CAA is a disease process that involves the deposition of β-amyloid protein in the walls of small brain arteries and arterioles that leads to vessel wall fragility and a propensity for rupturing [61]. Finally, ICH can also be secondary to structural lesions such as cavernomas or arteriovenous malformations; systemic disease such as hepatic cirrhosis or thrombocytopenia; or anticoagulant therapy [62].

Risk Factors

A risk factor for a disease is an entity that increases the chance of developing the specific disease. Stroke risk factors are often divided into non-modifiable and modifiable risk factors, where modifiable risk factors are potential targets for interventions that can reduce the risk of stroke. Since stroke is a heterogenous disease including both hemorrhagic and ischemic events, risk factors can have different size effects for different types of stroke [63]. Major stroke risk factors are presented in Table 1.

Table 1. Non-modifiable and modifiable risk factors for stroke

Non-modifiable risk factors	Modifiable risk factors
Age	Hypertension
Sex	Diabetes mellitus
Ethnicity	Atrial fibrillation
Genetics	Dyslipidemia
Previous stroke/TIA	Cigarette smoking
	Obesity, sedentary behavior
	Alcohol consumption
	Dietary factors
	Illicit substance use

Non-modifiable Risk Factors

Age is the major non-modifiable risk factor for stroke, and stroke risk doubles for every decade after the age of 55 years [64, 65]. Male sex is an overall risk factor for stroke and stroke incidence is around 30% higher among men [66]. However, due to longer life expectancy, lifetime risk of stroke is higher among women [67].

Furthermore, there are also disparities in stroke risk between ethnic groups, where both Hispanic and Black populations in the U.S. have higher stroke risk than White populations [68, 69]. Some of this disparity may be explained by differences in the prevalence of modifiable stroke risk factors [70].

Stroke also shows a high degree of heritability, wherein a family history of stroke increases stroke risk by approximately 30% [71]. Heritability varies between the main ischemic stroke pathogenetic mechanisms, in which about 40% of LAA stroke is explained by hereditary factors, 30% for CE and around 15% for SAO [72]. Monogenic conditions associated with stroke include cerebral autosomal dominant arteriopathy and subcortical infarcts and leukoencephalopathy (CADASIL); sickle cell anemia; and Fabry's disease [63], whereas new gene loci that entail higher risk of stroke are continually being uncovered [73]. These genetic causes of stroke are currently regarded as non-modifiable – but advances in gene therapy may open new therapeutic options in the future [74].

Modifiable Risk Factors

The recently updated INTERSTROKE study [75] identified 10 potentially modifiable risk factors that together account for roughly 90% of the population attributable risk (the proportion of the incidence of a disease that is due to a specific risk factor exposure) of stroke. Hypertension is the most important risk factor for stroke, contributing between 48-64% of the population attributable risk and increases the risk of both ischemic and hemorrhagic stroke [75, 76]. Diabetes mellitus is associated with a twofold risk of ischemic stroke [63, 77], and atrial fibrillation is a strong risk factor for cardioembolic ischemic stroke [63, 75]. Dyslipidemia is a risk factor for stroke, although there is conflicting evidence for different forms of dyslipidemia, and even a potential inverse relationship between hypercholesterolemia and hemorrhagic stroke [75, 78-80].

Among lifestyle risk factors for stroke, cigarette smoking has a dose-response relationship with risk of ischemic stroke, partly through long-term development of atherosclerosis [81, 82]. Furthermore, a recent meta-analysis confirmed body mass index (BMI) as an important stroke risk factor, that elicits its effect primarily via other risk factors such as increased blood pressure, dyslipidemia and elevated blood glucose [83]. On the other hand, regular physical activity is protective for stroke, also in part via effects on other risk factors such as blood pressure and diabetes mellitus [75, 84]. Psychosocial stress and depression have similarly been implicated as a risk factor for stroke [75, 85]. Meanwhile, low-moderate alcohol consumption has been suggested to be protective for stroke, even when attempting to adjust for so called "sick quitters", i.e. those who cease their alcohol consumption after the effects of long-term over-use have already occurred [86]. Nonetheless, high or episodic alcohol consumption is a risk factor for stroke [75]. Moreover, certain diets have been implicated in the reduction of stroke risk, for example the Mediterranean diet – in part via a reduction in blood pressure [87]. Finally, illicit drug use is

associated with both ischemic and hemorrhagic stroke through e.g. cerebral vasospasm, hypertensive crisis, or embolization upon use of intravenous substances [88].

In summary, stroke is a heterogenous disease with a complex background of risk factors and causes, that damage brain tissue and elicit disability or death for affected individuals. Consequently, the outcome of stroke can vary depending on the cause – and separate assessments of the different causes of stroke are important to estimate the clinical prognosis of stroke.

Clinical Presentation

Just as the causes and risk factors for stroke are heterogenous, stroke can affect multiple specialized and lateralized areas of the brain with different functions – and the clinical presentation of stroke can therefore vary greatly.

The brain's functions are topographically ordered and some functions, such as language, are also lateralized – i.e. the left and right halves of the brain have individual functions [89]. Stroke is a vascular disease, and symptoms therefore depend on which vascular territories of the brain are affected.

Symptomatology of Stroke by Vascular Territories

The anterior cerebral artery (ACA) supplies most of the cerebral cortex on the anterior medial brain surface, from the frontal lobes to the anterior parietal lobes [90]. This area also often includes the medial aspect of the sensorimotor cortex [90]. The typical symptomatology attributed to ACA lesions includes contralateral weakness of one side (hemiparesis), often affecting the contralateral leg the most [90]. When the frontal lobe is affected, apathy and apraxia can also occur [90].

The middle cerebral artery (MCA) supplies a large cerebral territory, most of the dorsolateral convexity of the brain, and is therefore a common vascular territory for ischemic events [90]. Loss of language functions (aphasia), contralateral hemiparesis and hemianesthesia, gaze preference toward the side of the lesion (conjugate deviation), and neglect are examples of symptoms from this vascular territory [90].

The posterior cerebral artery (PCA) supplies the cerebral cortex in the inferior and medial temporal lobes as well as the occipital lobe [90]. Lesions in the PCA territory typically cause a contralateral homonymous hemianopia, or smaller unilateral visual field defects [90]. Penetrating vessels from the PCA also supply the subcortical internal capsule which can cause contralateral hemianesthesia and/or hemiparesis [90]. Meanwhile, perforating arteries from the proximal PCA supply the midbrain

and thalamus which can lead to oculomotor palsy, pupil dilation, ataxia and impaired consciousness [91].

Deep structures of the brain such as the subcortical internal capsule, basal ganglia and the thalamus are supplied by, among others, the lenticulostriate arteries and the anterior choroidal artery [90]. Small lesions in these small vessels such as lacunar infarcts or deep intracerebral hemorrhage can cause contralateral hemiparesis due to the passage of the corticospinal tract through these deep cerebral structures, which is then, especially if the lesion is ischemic, called pure motor stroke, one of four well known lacunar syndromes [90]. Other lacunar syndromes include ataxic hemiparesis (one-sided incoordination as well as weakness), pure sensory stroke (contralateral sensory loss due to a thalamic lesion), and dysarthria-clumsy hand syndrome (due to a lesion in the internal capsule or pons)[90].

Branches from the vertebrobasilar arterial system provide blood supply to the brainstem and cerebellum [91], including cranial nerve nuclei throughout the brainstem. Thus, symptoms attributable to dysfunction from cranial nerves can be displayed in vertebrobasilar stroke – such as vertigo, double vision (diplopia), trouble articulating (dysarthria) and swallowing (dysphagia) [91]. The corticospinal and somatosensory pathways can also be damaged at the brainstem level, typically causing crossed symptoms (for instance ipsilateral sensation loss and contralateral weakness) [91]. Cerebellar lesions can cause vertigo, gait disturbances and incoordination (ataxia) [91].

Finally, despite the fact that these symptoms can help to localize the area of the brain that is affected, clinical examination alone cannot elicit whether the stroke is caused by an infarct or a bleed – and this is first able to be assessed via radiological or pathological examination [91].

Typical symptoms for various vascular lesions are visualized in Figure 5.

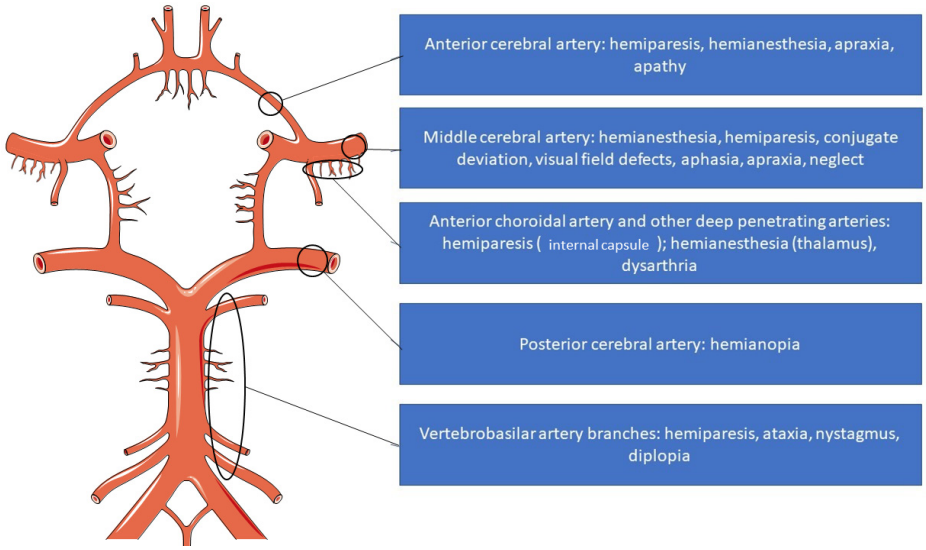

Figure 5. Examples of possible stroke symptoms according to cerebral vascular territories. Images modified from smart.servier.com. Licensed under a Creative Commons Attribution 3.0 Unported License.

Global Symptoms

Major lesions that lead to widespread tissue damage such as major MCA infarcts or brain bleeds can also lead to global disturbances of neurological function such as coma - via cerebral edema, increased intracranial pressure and herniation of intracranial structures [92]. Since subarachnoid hemorrhage irritates the meninges, its debut is often accompanied by a sudden onset of severe headache ("thunderclap headache") [92].

Measures and Classification of Stroke Symptoms

The Oxfordshire Community Stroke Project (OCSP) classification is a widely used clinical and research tool that categorizes ischemic stroke syndromes into 4 clinical subtypes: total anterior circulation infarct (TACI); partial anterior circulation infarct (PACI); lacunar infarct (LACI), and posterior circulation infarct (POCI), using clinical stroke patterns and their typical neuroanatomical locales as a basis [93].

The National Institutes of Health Stroke Scale (NIHSS) is a ubiquitous measure of stroke severity and neurological deficits, used both clinically and in research settings [94]. The scale considers global symptoms such as level of consciousness and orientation as well as visual disturbances, gaze preference, focal motor and sensory deficits, speech quality and articulation, and ataxia and neglect [94]. It is scored from 0-42 points, where zero indicates no neurological deficit, and the worst attainable score is 39 in a comatose patient [94]. NIHSS has been used as an outcome measure in seminal acute stroke treatment trials such as the NINDS trial

for intravenous thrombolysis [95] and MRCLEAN trial for mechanical thrombectomy [96]; and is recommended as a measure of stroke severity in epidemiological stroke studies [34].

Key predictors of a stroke diagnosis upon presentation of a neurological disorder in an individual include the determination of an exact onset time, history of focal neurological symptoms that can be anatomically localized with OCSP, neurological deficits according to NIHSS and signs of other vascular disease [97].

In conclusion, stroke can produce a wide array of clinical symptoms depending on which vascular territories and in turn which brain regions that are affected, ranging from focal sensorimotor disturbances to global neurological dysfunction such as coma. Certain measures are widely used to classify the clinical presentation of stroke. Persisting clinical symptoms after stroke and damage to different brain areas can lead to a variety of long-term consequences for survivors' function and quality of life that will be further discussed under *Functional Outcome*.

Acute Treatment

In the acute phase of ischemic stroke, the highest priority of treatment is to restore blood supply to the affected brain tissue to allow the penumbra area to recover. There are two main available treatments to achieve reperfusion, intravenous thrombolysis and mechanical thrombectomy [98].

Intravenous thrombolysis has been a mainstay in acute stroke treatment since the National Institute of Neurological Disorders and Stroke (NINDS) and European Cooperative Acute Stroke Study (ECASS) landmark trials in 1995 which established the efficacy of tissue plasminogen activator (tPA) in acute stroke [95, 99]. Following meta-analyses have established benefit of treatment in acute stroke up to 4.5 hours after debut of stroke symptoms, whereas more recent MRI and CT techniques have shown benefit in certain stroke cases also when time of symptom onset is unknown or up to 9 hours after symptom onset [100, 101]. Both intra- and extracranial hemorrhagic complications are the most feared complications of this treatment, and multiple absolute and relative contraindications to tPA treatment relate to risk of hemorrhagic events [29].

Mechanical thrombectomy emerged as a widespread acute treatment option in ischemic stroke in 2015 when multiple trials established the efficacy of thrombectomy treatment with stent retriever devices to remove the occluding embolus/thrombus from a major occluded brain artery [29, 96, 102, 103]. Thrombectomy is especially recommended in those with minimal or no pre-stroke disability, moderate-severe to severe stroke and occlusion of primarily the internal carotid artery or proximal middle cerebral artery with symptom onset within 6 hours

– and may also be indicated even up to 24 hours, depending on perfusion neuroimaging [104].

In the acute phase of stroke, emergent treatment of hyperglycemia and hypertension is also important since hyperglycemia is associated with worse clinical outcome, greater infarct growth and hemorrhagic conversion; while hypertension is associated with increased risk of symptomatic intracerebral hemorrhage – especially in conjunction with tPA treatment [105-107].

Intracerebral hemorrhage may need emergent surgical evacuation upon brainstem compression or hydrocephalus [108]; while subarachnoid hemorrhage may require treatment of vasospasm and early clipping or coiling of a ruptured aneurysm [109].

In conclusion, some acute therapies in stroke aim to stop ongoing brain damage by reperfusion of occluded brain vessels or by halting or evacuating ongoing bleeding, whereas some treatments aim to abate the effects of the brain damage, such as controlling glucose and blood pressure levels. Recent advances in acute treatment may have also affected stroke epidemiology and outcome, which necessitates their renewed study such as in the present thesis. Meanwhile, other treatment after stroke aims to decrease the risk of new stroke, which will be discussed henceforth.

Stroke Recurrence and Secondary Prevention

Recurrent Stroke

Stroke recurrence is a new stroke that occurs after the first-ever stroke event. A large 2011 meta-analysis of stroke recurrence showed a wide variation of recurrence rates, with substantial heterogeneity between studies. Pooled estimates of all stroke gave a recurrence rate of 11% within one year and 26% at 5 years [110]. The heterogeneity between studies may in part be due to the inclusion of both hospital-based and population-based studies [110], but also because of variation in the definition of stroke recurrence [111]. Previous definitions of recurrence stroke have attempted to exclude neurological deterioration due to the first-ever stroke event by only including new events occurring 28 days or more after first-ever stroke, or by excluding new events in the same vascular territory within 28 days [111]. However, this may lead to an underestimation of the risk of recurrent stroke, and the definition: "any recurrent stroke occurring >24 hours after the onset of the incident stroke, irrespective of vascular territory" has previously been recommended [111].

A more recent population-based British study of stroke recurrence reported 10% 5-year stroke recurrence, as well as a decrease in stroke recurrence rates from the 1990s to the mid-2000s [112]. Stroke recurrence rates appear to have subsequently remained unchanged in recent years [112], and there is a dearth of other current population-based studies of stroke recurrence in the available literature. Recurrence

rates over the last 18 years in a recent German study [113] are presented in Figure 6.

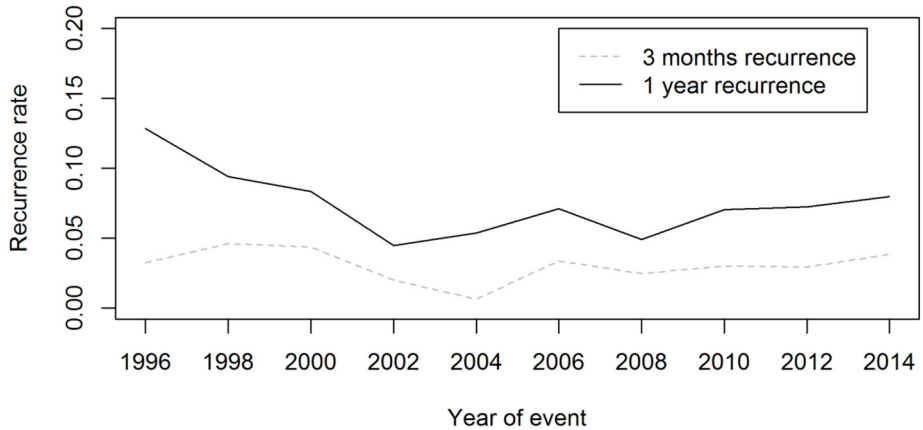

Figure 6. Temporal trends of crude 3-month and 1-year recurrence rates of stroke over 18 years in a German cohort. Reprinted from Stroke, Vol 51, Rücker et al., Twenty-Year Time Trends in Long-Term Case-Fatality and Recurrence Rates After Ischemic Stroke Stratified by Etiology, pp. 2778-2785. Copyright (2020) with permission from Wolters Kluver.

Among ischemic stroke pathogenetic mechanisms, LAA is associated with the highest risk of early recurrence [114], while cardioembolic stroke also has a high recurrence risk [112] and atrial fibrillation has been established as an independent general risk factor for stroke recurrence [115].

As for intracerebral hemorrhage, lobar hemorrhages recur in around 3-14% of cases within one year, whereas deep hemorrhages have a recurrence rate of approximately 2% per year [116, 117].

Secondary Prevention

The risk of recurrent stroke can be mitigated with several interventions targeting stroke risk factors, and improved treatment has contributed to the decrease in stroke recurrence over the last decades [118].

Antihypertensive treatment is recommended after the acute phase for IS and ICH patients, with an individualized treatment goal [119, 120]. Conversely, in the acute phase, blood pressure lowering should be limited due to the risk of decreasing cerebral perfusion to the damaged area of the brain [29]. Antiplatelet therapy is recommended in non-cardioembolic stroke – and in certain cases of minor stroke, initial double anti-platelet therapy reduces the early risk of major ischemic events [121, 122]. Intensive therapy of diabetes mellitus is recommended [123]; lipid-

lowering treatment is recommended with a goal of serum LDL <1.8 mmol/L for high-risk ischemic stroke patients [124, 125].

Among ischemic stroke with cardioembolic causes, patients with atrial fibrillation and stroke are recommended oral anticoagulant therapy with direct oral anticoagulants (DOAC) [126-128]. Original trials of anticoagulant therapy with warfarin showed a reduction of 42% in recurrent stroke and systemic embolism compared with antiplatelet medication with aspirin [126]. Recent studies have since shown non-inferiority or superiority as well as better safety profiles for several DOACs in stroke and atrial fibrillation [127, 128].

For ischemic stroke with LAA as pathogenetic mechanism, surgical carotid endarterectomy can reduce stroke recurrence rates among individuals with severe stenosis in the internal carotid artery [129].

The abovementioned interventions are the main secondary prevention treatments for stroke, as well as lifestyle management to address risk factors such as lack of physical activity, obesity and smoking [130]. Other specific stroke causes have specific therapeutic options, such as closure of patent foramen ovale in patients with non-lacunar stroke of undetermined cause [131].

Regarding ICH, the main component of secondary prevention treatment is management of hypertension, as well as risk assessment in case of a need of antithrombotic or anticoagulant therapy [108]. Contrary to in ischemic stroke, there are some indications that statins may be harmful after intracerebral hemorrhage [80], but evidence is lacking [108]. Statin therapy after ICH is therefore not routinely recommended [108]. In aneurysmal SAH, blood pressure control is recommended until obliteration of the offending cerebral aneurysm is possible via surgical (with clips) or endovascular (via coiling) methods, as early as feasible [109].

In summary, stroke recurrence rates have declined until recent years with improving secondary prevention strategies, but approximately one in ten still experience a new stroke within 5 years which entails a substantial risk for further loss of function or death. Knowledge of the risk of stroke recurrence among different pathogenetic mechanisms is vital to assess the clinical necessity of secondary prevention treatments.

Functional Outcome and Health-Related Quality of Life

Since stroke is a heterogenous disease that can affect several bodily functions and systems via its effect on the brain, there are a great deal of health problems that can arise for an individual after a stroke. Although preventing death is a major treatment goal in stroke care, high rates of disability in a chronic illness can cause a high burden of disease, commonly measured with disability-adjusted life years (DALYs)

– which attempt to quantify the amount of healthy years of life lost due to a disease [132]. Since a goal of medical treatment and care is to improve health, both death and disability need to be assessed and followed to ensure that medical care of a disease is meeting its targets [132].

Outcome Measurement

What is Health?

To assess the impact and burden of a disease in a population and to evaluate whether therapeutic interventions actually improve health requires an understanding of what health means. In 1948, the WHO proposed a definition of health as: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [133]. This definition has since been criticized as a too absolute definition that may contribute to overmedicalization [134], but no other universally accepted definition has been suggested since – and the complex subject of defining health is continually discussed across several scientific fields [135].

The International Classification of Functioning, Disability and Health

To be able to accurately describe and compare outcomes, as well as evaluating effects of treatment – common and universal definitions and measures are needed. There are a multitude of various outcome measures intended for use in chronic stroke, which can be classified using the WHO International Classification of Functioning, Disability and Health (ICF) [136]. The ICF classifies areas of health and disability into several domains and constitutes a framework for describing different areas of human functioning. A core set of ICF has been validated and deemed feasible as a framework to identify post-stroke problems in Swedish stroke survivors [137]. Three main levels of functioning are identified in the ICF:

1) Body function and structure

Body functions refers to physiological functions of body systems, including psychological functions, whereas body structure refers to anatomical parts of the body [136]. Under this level, domains such as voice and speech function, the structure of the nervous system and sensory functions and pain are measured. A problem in a body function or structure is referred to as an impairment and is one indicator of dysfunction/disability [136].

2) Activities

This level concerns the execution of tasks or actions [136]. Domains such as learning and applying knowledge, mobility and self-care, are ordered in this level. Activity limitations may also infer disability or dysfunction [136]

.

3) Participation

Participation concerns involvement in life situations such as communication, interpersonal relationships and community and social life [136]. Participation restrictions may also lead to dysfunction or disability [136].

These 3 levels of functioning are in turn affected by environmental and personal factors such as products and technology for aid, personal support and relationships, personal attitudes and prior experiences, as well as available services and systems for an individual with a health problem [136]. The following diagram (Figure 7) portrays the model of disability used in the ICF:

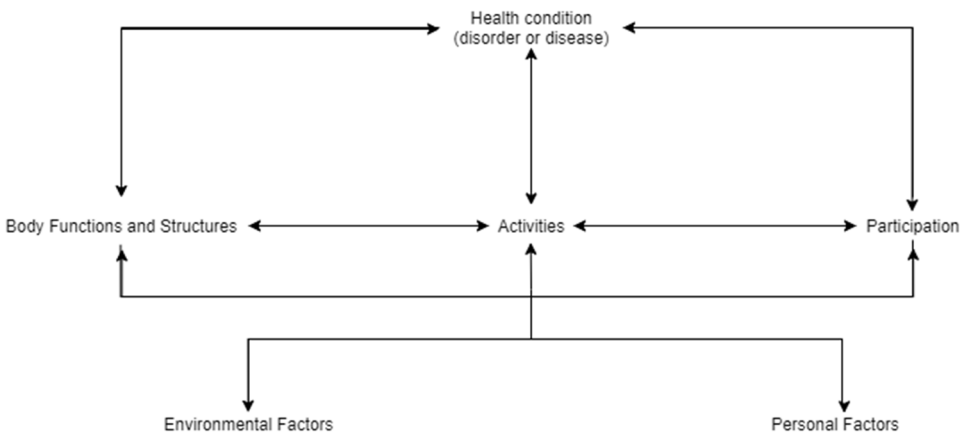

Figure 7. The biopsychosocial model of health and disability that is the basis for the International Classification of Functioning, Disability and Health (ICF). Modified from the World Health Organization, International Classification of Functioning, Disability and Health: ICF, 2001.

Considerations with Outcome Measures

The quality of instruments used to measure stroke outcome depends on the instrument's psychometric properties. These properties can describe how useful the results yielded from the outcome measure are to compare results between studies, to study specific problems isolated from other issues, or to follow outcome over time [138]. Common properties that need to be considered when choosing an outcome measure are presented in Table 2.

Table 2. Definitions and standards for a selection of psychometric properties for outcome measurements. Modified with permission from Salter et al, Evidence-Based Review of Stroke Rehabilitation. ESRSR 2013.

PROPERTY	DEFINITION	STANDARD
APPROPRIATENESS	How well the outcome measure being used matches the purpose of the study.	Depends on study purpose.
RELIABILITY	Refers to whether results are reproducible and internally consistent. Reproducibility depends on whether the score is affected by random error and is commonly tested with kappa statistics for test re-test reliability (stability of scores when a patient retakes the same test), and inter-observer reliability (stability of scores when the test is carried out by different evaluators). Internal consistency refers to how homogenous different items on the scale are, i.e. the correlation between different items that test similar concepts.	Test-retest or interreliability is considered excellent when kappa values are over 0.75 and poor when below 0.4 [139]. Internal consistency is considered poor when Cronbach's α is <0.7 [139].
VALIDITY	There are several different types of validity, but the term in general refers to how well the instrument measures the real-life intended outcome and can be estimated by comparing with another gold standard test and performing receiver operating characteristic (ROC) analysis.	ROC analysis area-under-curve values of above 0.9 are considered excellent and under 0.7 poor [140].
RESPONSIVENESS	Refers to the outcome measure's sensitivity to changes within patients over time. Floor or ceiling effects can affect responsiveness wherein if many participants receive the maximum or minimum score, there is no longer any margin for detecting change between tests.	Floor/ceiling effects are considered adequate if less than 20% of participants attain either the minimum or maximum score [140].
PRECISION	Refers to the number of distinctions within the scale, for example if it is scored 0-100 or is a dichotomous yes/no.	The necessary precision depends on the purpose of the measurement.
ACCEPTABILITY	Refers to how acceptable the testing is for participants. For instance if the testing itself represents a burden for the participant.	
FEASIBILITY	Refers to, among other things, how difficult or time-consuming the test is to perform, expense and disruption to clinical care.	

Alongside the abovementioned psychometric properties, it is also important to recognize that psychometric properties of an outcome measure can vary depending on which population is tested. For instance, reliability and validity can be excellent for a specific outcome measure when used in one disease setting but be poor in others [138].

Outcome After Stroke

There are various functional impairments after stroke that can affect body functions, activities and participation, such as paresis, visual impairments, aphasia, cognitive impairments, depression and fatigue [141-145]. No single outcome measure

encompasses the whole experience of post-stroke outcome, and several tools are used to estimate different domains of health and disability.

Neurological Impairment

Neurological impairments such as aphasia, paresis, visual impairment, neglect or loss of sensation are common stroke symptoms and are almost universally measured with the NIHSS at first contact with healthcare [94], which has previously been described in this thesis. NIHSS has excellent reliability when assessed by trained adjudicators, and scores at baseline are strongly correlated with both initial infarct volume in ischemic stroke and post-stroke functional outcome [146-148]. Even among those who receive acute reperfusion therapies, over 50% are left with disabling residual neurological impairment [100, 149]. Since the NIHSS assesses several domains of stroke-specific dysfunction, it has recently been increasingly implicated as a valuable screening tool for recovery assessment as well as its established role in the acute phase [150].

Post-Stroke Epilepsy

Cerebrovascular lesions are the most common cause of secondary epilepsy in adults and are particularly associated with hemorrhagic stroke or large IS lesion sizes or TACI as clinical IS syndrome [151]. Post-stroke epilepsy accounts for around one in ten epilepsy diagnoses [151], and has been shown to negatively affect patient-reported vitality and physical and social functioning [152].

Functional Outcome

Functional outcome aims to describe a stroke survivor's independency in daily life and their activities of daily living (ADL), and thus depends on various body functions such as motor skills, language, and cognition [153]. ADL encompasses basic functions such as dressing oneself, mobility and toileting, as well as more complex daily activities such as shopping, transporting oneself or cooking meals. [153]. The most used outcome measures for functional outcome after stroke are the modified Rankin Scale (mRS) and Barthel Index (BI) [154, 155].

The mRS is a global scale of function and activities with a single item graded from 0-6, where 0 indicates no symptoms; 1 indicates symptoms but no significant disability; 2 indicates slight disability and loss of activity while still being independent; 3-5 indicate moderate, moderately severe and severe disability, respectively, and 6 indicates death [154]. For ischemic stroke, the mRS is often dichotomized into 0-2 as favorable outcome and 3-6 as poor outcome [156]. Meanwhile, in ICH trials, 0-3 is sometimes considered favorable [157]. Reliability for the mRS has been reported as excellent for both test-retest and inter-rater reliability [158], while validity studies have shown excellent concurrent validity when compared with several other outcome measures, including BI and infarct

volume in ischemic stroke [157, 159]. However, there are concerns over the scales interobserver variability and reproducibility, as well as an ongoing debate on how best to statistically analyze results in different study settings [157]. Furthermore, the mRS is a global measure of functioning and is liable to confounding from other conditions, as well as being unable to discern which specific problems are causing loss of function [157, 160].

The BI measures functional independence in ADL, such as feeding, bathing, grooming, bladder and bowel control and ambulation [159]. The BI is scored as a summed aggregate of 10 items with between 0-5 to 0-15 points per item, with a total score of 100 points [155]. Higher scores indicate a greater degree of functional independence [159]. The BI has excellent reliability [161] and concurrent validity [162] but has significant ceiling effects in highly functional individuals that yields poor responsiveness [162].

Previous studies have demonstrated rates of favorable functional outcome of between 59-69% among ischemic stroke survivors at 5 years, and predictors of poor functional outcome in the long-term include age, diabetes mellitus, post-stroke cognitive impairments and psychiatric comorbidities [141, 144, 163]. Comorbidities are also associated with worse functional outcome after stroke, and are commonly quantified with the Charlson Comorbidity Index (CCI), which gives a weighted score to 12 comorbid conditions for a total score between 0-24, where 24 denotes highest comorbidity – and has been validated in stroke [164, 165]. Meanwhile, at 10 years after stroke, most survivors are functionally independent in ADL, but around 15% have major dependency, defined as scores from 0-55 on BI [144].

Cognitive Impairment

Post-stroke cognitive impairment (PSCI) is another common sequela of stroke that occurs in between 7-41% in the first year after stroke, depending on whether pre-stroke cognitive impairment is included or not [166], and occurs similarly across pathogenetic mechanisms of ischemic stroke [167]. At ten years in a Swedish stroke cohort, 46-61% had PSCI, but these prevalence estimates depend on both the outcome measure used and cut-off values [168]. Predictors of PSCI include age, female sex, lower education, pre-stroke cognitive impairment as well as diabetes mellitus and atrial fibrillation [166]. PSCI is also associated with activity limitations and participation restrictions across several cognitive domains such as neglect, attention, visuospatial ability, language, memory and executive skills; as well as functional outcomes including basic and complex ADL [169].

The Mini-Mental State Examination (MMSE) is a commonly used cognitive screening test for detecting dementia that is also frequently used in stroke research [170, 171]. However, the MMSE has weaknesses in detecting mild cognitive deficits due to ceiling effects, as well as executive dysfunction which may be an impairment that is more specific for stroke [171]. A more recently developed

measure of cognitive outcome, the Montreal Cognitive Assessment (MoCA) has higher sensitivity for executive function deficits and mild cognitive impairments and may be more suitable in studies of long-term cognitive outcome after stroke [168, 172]. MoCA examines attention, concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientations over 10 items, and is scored between 0-30, where 30 indicates no cognitive impairment. MoCA has excellent reliability regarding consistency and test-retest reliability and has excellent concurrent validity with MMSE [172].

Post-Stroke Depression

Depression, anxiety and other affective disorders are common after stroke, affecting about one third of stroke survivors at any one time after stroke [173-175]. This rate is significantly higher than the background prevalence of depressive disorders [176], and some evidence suggests that post-stroke depression (PSD) has an underlying unique neurobiological cause [177]. Physical disability, stroke severity, pre-stroke depression and cognitive impairments are independent predictors of PSD [178, 179], and PSD is associated with participation restriction and poor functional outcome after stroke [180].

There are many screening instruments for depression available, but a prior meta-analysis has suggested 3 optimal measures for PSD screening: The Center of Epidemiological Studies-Depression Scale (CESD); the Hamilton Depression Rating Scale; and the Patient Health Questionnaire (PHQ-9) [181]. The PHQ-9 [182] is shorter than many other depression screening instruments while showing excellent reliability and excellent convergent validity when compared with the more comprehensive and time-consuming Beck Depression Inventory [183]. The PHQ-9 is a patient-reported outcome measure (PROM) that consists of 9 items ranked on a severity scale from 0-3 and includes all 9 diagnostic criteria used in the DSM-IV [184].

Post-Stroke Fatigue

Post-stroke fatigue (PSF) is a common consequence of stroke, with a prevalence that varies between 25-85% in studies, partly due to heterogeneity of outcome measures [145]. Reported clinical features of PSF include reduced mental capacity and a reduction in energy needed for daily activities as well as self-control and emotional instability [185]. Moreover, forty percent of stroke survivors report fatigue as their worst or one of their worst symptoms [186]. PSF has been associated with poor functional outcome, shorter survival and limitations in complex ADL [187-189]. PSF is also associated with depression, where studies have shown that 29-38% of individuals with severe fatigue are also depressed [186, 190]. There is currently no evidence to support any intervention to treat post-stroke fatigue [191].

There are several fatigue-specific outcome measures that are validated in stroke, but a prior comparative study has recommended Fatigue Assessment Scale (FAS) as a

patient-reported outcome measure [192]. FAS has low internal consistency since the items relate to different elements of fatigue, but among the four tested fatigue scales (the three others were: the SF36v2 vitality component, the fatigue subscale of the Profile of Mood States and the general subscale of the Multidimensional Fatigue Symptom Inventory) in this comparative study, it had best test-retest reliability and high validity as well as good feasibility [192]. The most used fatigue measurement in stroke is the Fatigue Severity Scale (FSS), which was excluded from comparisons in the comparative study due to insufficient face validity [192]. A more recent review article has shown that there is a lack of PROM's that encompass multiple dimensions of PSF [193].

Health-Related Quality of Life and Patient-Reported Outcome Measures

Whereas most of the abovementioned outcome measures target specific domains of functioning, activities or participation based on empirical observation, patient-reported outcomes and assessments of quality of life are vital to reveal real-life treatment outcomes and identify the range of problems that stroke patients experience [194]. Health-related quality of life (HRQoL) refers to "how health impacts on an individual's ability to function and his or her perceived well-being in physical, mental and social domains of life" [195]. HRQoL assessments are commonly used in economic evaluations of treatment interventions, together with survival data, as quality-adjusted life-years (QALYs) – a calculated measure of HRQoL and survival where one QALY equals one year in perfect health, and 0 denotes death [196]. Moreover, HRQoL is increasingly used as one of the outcome measures in clinical stroke trials [197].

A proposed conceptual model of HRQoL is shown in Figure 8, where a causative chain from biological dysfunction leads to an effect on overall quality of life [198].

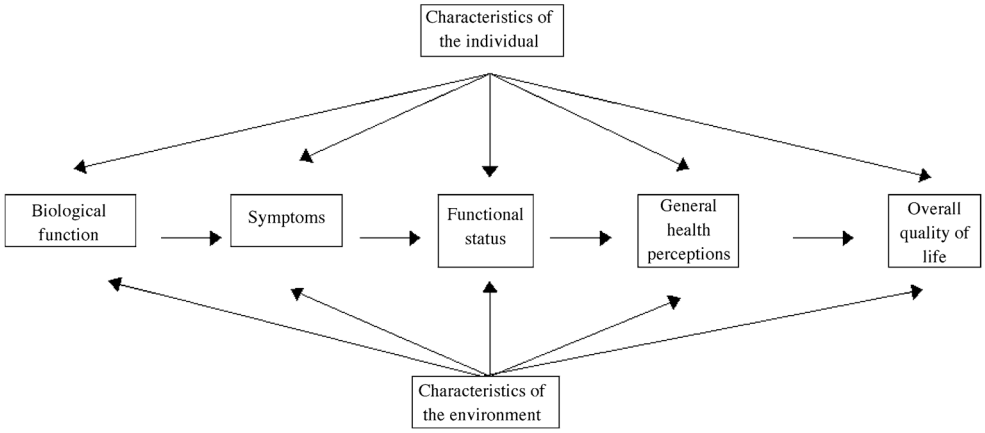

Figure 8. Revised Wilson and Cleary conceptual model for health-related quality of life. Reprinted with permission from J Nurs Scholarship, Vol 37, Ferrans et al. Conceptual model of health-related quality of life, pp. 336-342. Copyright (2005) with permission from John Wiley & Sons.

HRQoL after stroke is associated with age, sex, education, socioeconomic aspects and depression as well as the level of functional outcome [199-201]. At 5-7 years post-stroke, 20-23% have very poor HRQoL according to prior studies [202, 203].

HRQoL is invariably a patient-reported outcome (PRO), that has been defined as "any report of the status of a patient's health condition that comes directly from the patient without interpretation by a practitioner or anyone else" [204]. Patient-reported outcome measures (PROM) are increasingly used as a source of data in research, clinical practice and quality registers [204]. PROMs can give valuable information on multiple domains of functioning, disability and health, and can either be generic or specific for the disease being studied [204]. A selection of PROMs that measure HRQoL are listed below.

The Short-Form Health Survey (SF-36)

The SF-36 is a widely used generic PROM used to assess HRQoL in a general population [205]. It consists of 36 items over 8 different domains (physical functioning, physical role limitations, bodily pain, general health perceptions, energy/vitality, social functioning and emotional role limitations) [205] and has adequate-excellent overall reliability and validity in stroke [206, 207], albeit with significant floor and ceiling effects [208].

EuroQoL-5D (EQ-5D)

EQ-5D is another widely used PROM that assesses 5 domains of health: mobility; self-care; activities; pain; and anxiety and depression. Each domain has either 3 or 5 levels of discrimination in different versions of the EQ-5D (EQ-5D-3L or EQ-5D-5L) – and both versions have been validated for stroke [209, 210]. The EQ-5D also

contains a visual analogue scale of overall health status that is ranked from 0 (worst possible health) to 100 (best possible health) [209]. The EQ-5D has shown adequate reliability and validity in stroke [209].

Stroke Impact Scale (SIS)

The SIS is a stroke-specific PROM that assesses 8 domains: strength; hand function; basal and complex ADL; mobility; communication; emotion; memory; and participation [211]. Each domain consists of several items that are rated on a 5-point Likert scale [211]. Scores are then aggregated for each domain to produce a score from 0-100 for each domain, where 0 is the worst outcome, and 100 the best [211]. Additionally, the SIS also contains a final item where patients report their perception of their stroke recovery from 0-100 [211]. The SIS has excellent concurrent validity upon comparison with multiple outcome measures across each domain, and adequate reliability [211].

In conclusion, stroke outcome is multi-faceted, and a comprehensive evaluation is needed to measure and address the multitude of health problems that may be experienced both short- and long-term. The ICF provides a conceptual framework to assess and identify problem areas, and PROMs can also increase the acuity of our view of stroke patients' experiences. Studies that include PROMs and assess multiple facets of post-stroke consequences are needed to fully assess and improve life after stroke.

Stroke Recovery

Stroke survivors' outcome in the long-term is also dependent on the recovery phase. Spontaneous recovery processes in stroke are time-dependent, i.e. different levels of recovery are expected at different times after the injury – at least for motor symptoms that are the most studied symptoms regarding recovery [212]. Plausible mechanisms for spontaneous stroke recovery include endogenous brain recovery mechanisms, e.g. increased levels of growth factor substances, neurogenesis, angiogenesis, vascular remodeling, synaptogenesis, dendritic growth and axonal remodeling [212, 213]. Furthermore, compensatory mechanisms such as altered neuronal network interactions, increased activity in distant brain regions connected to the injured area, and recruitment of neurons of the contralateral hemisphere. [212]. These modifications in the organization of neurons in the central nervous system, either physiologically during an individual's life span or adaptively after brain injury, are collectively referred to as neuroplasticity. Within hours after stroke, neuronal plasticity-enhancing mechanisms lead to the formation of new synapses [212]. In animal studies, these mechanisms are most active up to 60 days post-infarct [214], and human studies have identified a 3-6-month period of enhanced neuroplasticity [215].

Prior studies of human motor recovery after stroke have shown a trajectory wherein recovery occurs in the first few months after an injury and reaches static levels thereafter [216]. A schematic figure of this trajectory is shown in Figure 9.

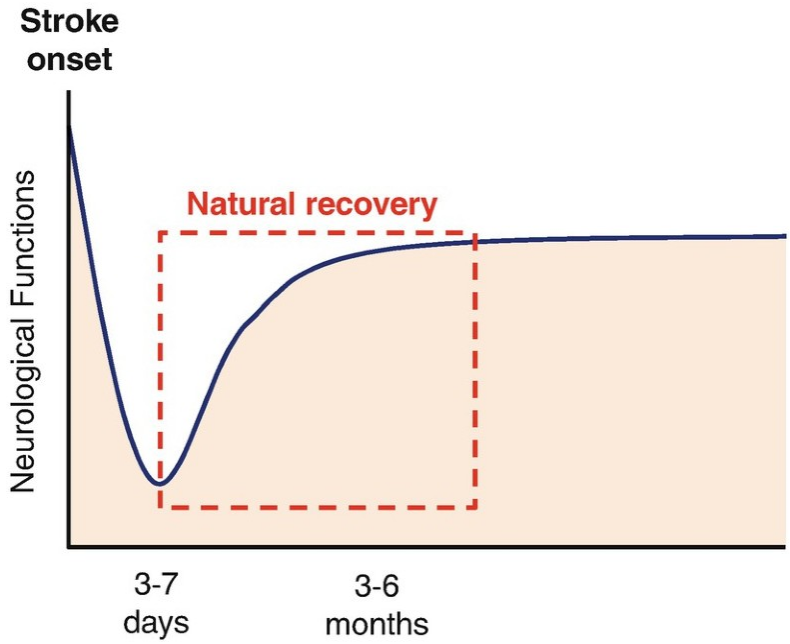

Figure 9. Schematic illustration of spontaneous recovery after stroke. Reprinted with permission from Koh SH. (2020) Mechanism of Recovery After Stroke. In: Lee SH. (eds) Stroke Revisited: Pathophysiology of Stroke. Stroke Revisited. Springer, Singapore. Copyright (2020) with permission from Springer Nature.

Due to this time distribution of recovery, stroke is commonly divided into phases: hyperacute (24 h); acute (7 days); subacute (3-6 months); and chronic stroke (after 6 months) [213]. However, recent studies are challenging this critical time window of recovery after stroke and suggest that the recovery period may be extended up to a year and possibly more [217].

Stroke Rehabilitation and Treatment in the Chronic Phase

Aside from secondary prevention of a new stroke after a first-ever stroke, there are some treatment modalities that have shown positive effects for augmenting recovery or ameliorating long-term consequences.

Regarding motor function, physical rehabilitation is effective for improving motor function, balance and walking speed and the effect persists after the intervention [218]. However, robust evidence on the best rehabilitation approach is lacking [218].

Meanwhile, aphasia after stroke can be treated with behavioral speech and language therapy with well-documented effect [219], whereas some studies have shown treatment effects with transcranial direct current stimulation, as well as with donezepil or memantine [220].

Post-stroke neglect may be treated with behavioral therapy such as prism adaptation, while some trials also show effects of non-invasive brain stimulation [221, 222].

For post-stroke mood disorders such as depression, antidepressant medication such as SSRIs may be effective, while exercise, counseling, and transcranial magnetic stimulation have shown benefit in treatment studies [223].

Current treatment options to alleviate PSF in the chronic phase of stroke are lacking, and prior randomized controlled trials have not revealed any treatment options with robust efficacy for treating PSF [191].

A prior treatment trial for cognitive impairments after stroke has shown some benefit on cognitive outcomes with escitalopram [224].

Finally, stem cell therapy is a developing field of research for possible treatment of motor and cognitive function in the chronic stage post-stroke [225].

While these potential treatments have shown effects in trials, many have yet adequately reached clinical practice or the patients living with chronic stroke. As of now, a recent study from the Swedish Stroke Register showed that a fifth of stroke survivors perceive unmet rehabilitation needs at 1 year post-stroke [226].

In conclusion, as of now treatment options are lacking for many domains of post-stroke functioning and disability, which further emphasizes the demand for a decrease of the burden of first-ever stroke, identifying problems after stroke that are important and debilitating for patients, and identifying treatment options for chronic stroke symptoms and impairments.

Knowledge Gaps

- Stroke epidemiology is continually changing, with altered primary and secondary prevention treatments as well as an aging population and increased post-stroke survival all contributing to differences in the prevalent stroke population. Continuous, preferably population-based epidemiological research from several geographic areas is needed to evaluate preventive treatment effects and inform policymakers.
- Since there is a growing trend towards using quality register data as estimates for epidemiological research and epidemiological trends, it is important to continually ascertain that these quality registers accurately portray the studied population. This information is a prerequisite for safely continuing to use these data as a valid complement to full-scale population-based studies.
- Recent population-based studies of long-term stroke outcome are scarce, as well as detailed data on patterns of stroke recurrence and causes of death. As stroke treatment and our population constitution changes, the way stroke recurs and leads to death may also change. Information about stroke recurrence and death after stroke is important for prognosticating outcome after stroke for patients, as well as for policymakers.
- Similarly, comprehensive studies of long-term outcome after stroke, including multiple domains of functioning and disability and "hidden" impairments such as PSD and PSF are needed to capture the range of post-stroke outcomes. Patient-reported data is also needed to identify patients' problem areas and direct research focus and treatment development to areas that mean the most to chronic stroke patients.

Aims

The overall aim of this thesis was to assess and describe the population-based epidemiology and outcome of stroke in our region of Southern Sweden, including comparisons with two local stroke registers.

The specific aims were:

- To examine population-based stroke incidence and early case-fatality rates in southern Sweden (Paper I)
- To explore temporal trends in stroke incidence and early case-fatality since the beginning of the millennium (Paper I)
- To provide new information on the completeness of case ascertainment in local hospital-based stroke registers (Paper II)
- To assess the effect of different approaches to case ascertainment in stroke registers on the risk of selection bias (Paper II)
- To investigate population-based 3-year survival, causes of death and recurrence after stroke (Paper III)
- To compare stroke survival in our study area with previous estimates from the last decades (Paper III)
- To assess long-term functional outcome and health-related quality of life after first-ever stroke (Paper IV)
- To examine predictors for poor functional outcome and HRQoL, and associations between various domains of outcome (Paper IV)

Methods

All papers in this thesis (I-IV) are based on a population-based sample of first-ever stroke between 2015-2016 in 8 municipalities (specified below) in southern Sweden with comparisons with prior studies from the same area. An overview of the methodological characteristics of the four studies are shown in Table 3.

Table 3. Overview of study populations in the four papers in the thesis

	PAPER I	PAPER II	PAPER III	PAPER IV
STUDY PERIODS	2001-2002; 2015-2016	2015-2016	1983-1985; 1993-1995; 2001-2002; 2015-2016	2015-2016
STUDY AREA	Eight municipalities surrounding Skåne University Hospital, Lund, Sweden			
PATIENTS	413	400 (excluding SAH)	400 (excluding SAH)	400 (excluding SAH)
CASE ASCERTAINMENT	Prospective case ascertainment through Lund Stroke Register (LSR) and Riksstroke, retrospective case ascertainment via the National Patient Register, primary care, outpatient clinic and autopsy registers.			
STUDY FOCUS	Temporal trends in stroke incidence and early case-fatality	Comparisons of case ascertainment and risk of selection bias in hospital-based stroke registers	Survival, causes of death and stroke recurrence at 3 years post-stroke	Functional outcome and health-related quality of life at 3-4 years post-stroke
STUDY DESIGN	Observational cohort study			
BASELINE DATA SOURCES	Prospectively collected baseline data from LSR and Riksstroke and retrospective medical record review			
OUTCOME ASSESSMENTS	Early case-fatality: Swedish Population Registry	Comparisons between cohorts	Survival and causes of death: Swedish Population Registry & Swedish Causes of Death Register; Stroke recurrence: Medical record review.	3-4-year follow up assessment of health-related quality of life, functional outcome, post-stroke depression, post-stroke cognitive impairment & post-stroke fatigue

Study Area and Population

The study area (Papers I-IV) comprises the 8 municipalities (Lund, Burlöv, Lomma, Staffanstorp, Kävlinge, Eslöv, Höör, and Hörby) that constitute the local catchment area of Skåne University Hospital in Lund, Sweden (SUS Lund). The area had a

total population of 274,239 inhabitants as of December 31, 2015 [227]. At the same time-point 8% of the population were older than 75 years, and 50% were female [227].

The study area is serviced by one hospital, SUS Lund, a local public hospital with emergency facilities; as well as 27 primary care centers, 9 of which are privately owned. Acute stroke patients in the area are predominantly treated at the stroke unit in the Department of Neurology at SUS Lund [228].

In Paper I, incidence and case-fatality in 2015-2016 is compared with data from the same area in 2001-2002. As of December 31, 2001, the area had a total population of 234,505 inhabitants, of which 7% were older than 75 years and 50% were female. Population data for incidence calculations in Paper I were obtained from Statistics Sweden [227].

Meanwhile, in Paper III, survival rates from 2001-2002 and 2015-2016 are compared with earlier studies from the same area in 1983-1985 and 1993-1995. In December 1983, the study area was comprised of 200,191 inhabitants, 6% were older than 75 years, and 51% were female [229]. Finally, among the 224,126 inhabitants in the area as of December 31, 1993: 7% were older than 75 years and 50% were female [227].

Case Ascertainment and Data Sources

In line with prior recommendations for population-based stroke studies, data was collected from multiple overlapping sources, including both prospective ("hot pursuit") and retrospective ("cold pursuit") methods [34]. The inclusion and exclusion criteria for the thesis cohort are listed below.

Inclusion Criteria

- Age ≥18 years at stroke onset
- First-ever stroke according to the WHO definition [12] between March 1, 2015 and February 29, 2016, including: i) IS, ICH and SAH (Paper I); or ii) IS or ICH (Papers II-IV)
- Resident of the local catchment area of SUS Lund at stroke onset

Exclusion Criteria

- Iatrogenic (stroke within 7 days of a procedure where it is deemed likely that the procedure caused the cerebrovascular event upon case review) or traumatic stroke
- Prior stroke

To assemble the population-based cohort on which this thesis is based, the abovementioned inclusion and exclusion criteria were applied to several overlapping data sources, that are presented below.

Lund Stroke Register (LSR)

The LSR is a local, ongoing, prospective and longitudinal observational stroke study that has been in operation since March 1, 2001. The study area and population studied in the current thesis is the same as the LSR's study area and population.

In LSR, research nurses perform daily weekday screenings of patient lists including all patients seen at the Emergency Department, as well as inpatient and outpatient lists at the Department of Neurology, SUS Lund. First-ever IS, ICH and SAH cases are all included in LSR, provided they meet the WHO definition of stroke [12] or TIA with visible acute ischemic lesions on MRI that correspond to the symptomatology. Cases are reviewed and validated on a case-by-case basis, and no specific stroke-related ICD-10 diagnosis codes are necessary for inclusion. To exclude those with previous stroke, LSR research nurses ask patients for previous stroke events, review medical records and search for previous registrations in LSR patient lists. Iatrogenic and traumatic stroke cases are also excluded in LSR, and iatrogenic stroke is defined as a stroke within 7 days of a procedure where it is deemed likely that the procedure caused the cerebrovascular event upon case review.

Oral and/or written informed consent is also required for inclusion in LSR; and since the LSR also studies, among other fields, genetic risk factors for stroke – patients are simultaneously asked for consent for blood samples and information on family history of cerebrovascular disease. If patients are unable to provide informed consent, their next-of-kin are consulted about inclusion in the study.

Riksstroke

Riksstroke is a national hospital-based stroke register that receives data on stroke patients from all 72 Swedish hospitals that provide acute stroke care [230]. At SUS Lund, Riksstroke includes stroke patients through continuous screening of patients admitted to the neurology wards. Furthermore, retrospective screening is performed monthly among all patients admitted to the hospital for stroke-related ICD-10 diagnosis codes – those with codes for IS (I63), ICH (I61) and unspecified cerebrovascular events (I64) are eligible for inclusion, but SAH cases were excluded prior to 2020, alongside iatrogenic cases. TIAs are also registered in Riksstroke, separately from stroke [230]. Included patients are informed of their inclusion in Riksstroke as a hospital-based quality register – and can opt out upon non-consent.

A comparison of case ascertainment routines in LSR and Riksstroke is shown in Table 4.

Table 4. Comparison of case ascertainment procedures in LSR and Riksstroke

	RIKSSTROKE	LSR
DEFINITION OF STROKE	• Based on WHO definition of stroke • Does not include subarachnoid hemorrhage • Does not include traumatic stroke • Includes iatrogenic stroke • Includes TIA in a separate domain • Time-based definition of TIA • Registers first-ever and recurrent stroke	• Based on WHO definition of stroke • Includes subarachnoid hemorrhage • Does not include traumatic stroke • Does not include iatrogenic stroke • Includes TIA with acute cerebral infarct on MRI corresponding to focal neurological symptoms • Time and imaging-based definition of TIA • Only registers first-ever stroke
SCREENING METHODS	• Prospective screening of neurological wards • Retrospective screening of Emergency Department visits and admissions • No screening of outpatient visits • No screening of primary care visits • No screening of autopsy registers	• Prospective screening of neurological wards • Prospective screening of Emergency Department visits and admissions • Prospective screening of Dept of Neurology outpatient visits • No screening of primary care visits • No screening of autopsy registers
CASE VALIDATION	Based on ICD-10 diagnosis codes	Based on ICD-10 diagnosis codes followed by case-by-case validation
CONSENT	Opt-out consent	Consent-based inclusion

The Swedish National Patient Register (NPR)

The NPR is a national Swedish database that is maintained by the Swedish National Board of Health and Welfare (in Swedish: Socialstyrelsen) [231]. The NPR includes information regarding all in-patient care in Sweden, as well as hospital-based outpatient doctor visits from both private and public caregivers [231]. However, primary care is not covered in the NPR [231].

The register is based on ICD-10 diagnosis codes, and its data is often used for validity assessments in national quality registers to assess their coverage of hospitalized patients.

Primary Care Databases

To detect stroke cases that were solely handled in the study area in primary care, a retrospective search was also performed in a regional database administered by Region Skåne, the regional health authority in Skåne, southern Sweden and of which SUS Lund is a part. The studied database registered all primary care visits in the study area, as well as all outpatient clinic visits at SUS Lund, irrespective of specialty clinic. All ICD-10 diagnosis codes registered in the medical record at the visit are also recorded in the database. A search was performed in the database of ICD-10 diagnosis codes G45, G46, G81, G83, or I60-69, and Swedish personal identification numbers could be used to link cases from the database to electronic medical records. Visits between March 1, 2015 and April 31, 2016 were screened, to also include stroke cases that occurred during the study period but where medical care might have been delayed.

Due to regulatory restrictions, access to the records of 9 privately run primary care centers (out of 27 in total) was denied.

Autopsy Registers

The Department of Pathology, and the Department of Forensic Medicine at SUS Lund compiled lists of autopsies with a date of death during the study period and autopsy findings of acute IS, ICH or SAH. Autopsy reports and medical records were linked via personal identification numbers.

Swedish Population Register

The Swedish Population Register is a nationwide register administered by the Swedish Tax Agency, and includes information on name, current address, personal identification number and date of death. When a person is declared dead in Sweden, a certificate is submitted to the Swedish Tax Agency – and it is estimated that 93% are reported within 10 days, and 100% within 30 days [232].

Swedish Causes of Death Register

Upon a person's death in Sweden, a form is also submitted to the National Board of Health and Welfare for registration in the Swedish Causes of Death Register [233]. Alongside the deceased's personal identification number and date of death, the Swedish Causes of Death Register also contains information on the direct cause of death (e.g. pneumonia), chain of events leading to death (e.g. hemiplegia) and underlying cause of death (e.g. stroke) and contributing causes of death based on ICD-10 diagnosis codes [233]. The causes of death data are dependent on the

reporting physician, but prior comparisons with systematically reviewed medical records have shown high levels of agreement [233]. However, causes of death may be less accurate among the elderly [234].

Data Linkage

Data on individual cases could be linked across the abovementioned data sources due to unique Swedish personal identification numbers, that are assigned to everyone who lives in Sweden and are kept throughout life [232].

Population-based Cohort (LSR PopR)

To assemble the cohort that this thesis is based on (Papers I-IV), the author (JA) first reviewed medical records of all individuals registered in LSR between March 1, 2015 and April 29, 2016 for inclusion in the present study. However, only first-ever stroke cases with symptom debut between March 1, 2015 and February 29, 2016 were included. The Riksstroke database was cross-referenced using personal identification numbers with the LSR database to exclude those who had already been registered in LSR but deemed ineligible, and those who were already included in LSR. Remaining Riksstroke patients' medical records were then reviewed for inclusion in the population-based cohort. Subsequently, primary care databases were cross-referenced with the current cohort and after excluding subjects already included, the remaining primary care medical records with stroke-related ICD-10 codes were reviewed for inclusion. Finally, lists of autopsied patients with possible stroke were reviewed both via medical records and autopsy reports for eligibility.

Prior to Paper II, the NPR was also reviewed for potential stroke patients, after similar cross-reference with the original cohort. One additional patient was included via the screening of NPR, yielding a total number of patients of 414, including SAH. For Papers II-IV, however, SAH (n=14) was excluded – leaving 400 patients in total. Subsequently in Paper III, cause of death data was also included from the Swedish Causes of Death Register. An overview of data sources used in the papers included in this thesis is presented in Table 5.

Table 5. Data sources used in the thesis's four papers

	PAPER I	PAPER II	PAPER III	PAPER IV
LSR	X	X	X	X
RIKSSTROKE	X	X	X	X
PRIMARY CARE DATABASES	X	X	X	X
AUTOPSY REGISTERS	X	X	X	X
NPR		X	X	X
SWEDISH POPULATION REGISTER	X	X	X	X
SWEDISH CAUSES OF DEATH REGISTER			X	

Prior Epidemiological Studies (Paper I and III)

In paper I, stroke incidence in 2015-2016 is compared with rates from a previous cohort in the same study area from 2001-2002 [228]. The 2001-2002 cohort is population-based with a very similar case ascertainment methodology to the present study. However, one difference between studies is that one primary care district in our study area (Orup, 56,565 inhabitants in 2001) could not be screened for stroke cases in 2001-2002 due to the absence of computerized medical records at that time [228].

In paper III, survival rates are compared with cohorts from 1983-1985, 1993-1995, and 2001-2002. The two earliest cohorts are based on the same study area, but are primarily hospital-based and not truly population-based [229, 235].

Follow-up Procedure

Papers I and II

In papers I and II, the only follow-up performed after baseline case detection was 28-day case fatality using the Swedish Population Register as noted above. Baseline characteristics were collected through medical record review. The assessed baseline characteristics are explained in the later section "Definitions and Clinical Assessments".

Papers III and IV

Data in papers III and IV are in part derived from the follow-up substudy Lund Stroke Register – Population and Recovery (LSR PopR), wherein the population-

based cohort from papers I and II were followed-up regarding stroke outcome at 3-4 years post-stroke.

Firstly, a check was performed in the National Population Register to determine if participants were alive at the start of follow-up in 2018. Stroke survivors were then contacted via telephone to attempt to book a one-hour follow-up appointment at the outpatient clinic of the Department of Neurology, SUS Lund; or at the patient's home if they were unable to attend a clinic visit. If the individual was not reachable via telephone after two attempts, a letter with an invitation to participate in the study was sent to the individual's home address. If a stroke survivor did not wish to attend a physical follow-up meeting, they were asked to answer available questions over the telephone. Attempts were made to ideally book a follow-up assessment within one month before or after the date exactly 3 years after the first-ever stroke event.

Clinical follow-up sessions adhered to a pre-specified protocol of questions and clinical outcome assessments and were performed by four different physicians in total, including the thesis author (JA).

Furthermore, for baseline LSR and Riksstroke participants and those who were deceased at follow-up, medical record review was performed to detect stroke recurrence based on the original given consent. For those who had not previously consented to LSR or LSR PopR, consent was sought for medical record access. Medical record review to detect stroke recurrence was only performed in hospital-based medical records, and primary care databases or autopsy registers were not surveyed.

Clinical Assessments and Definitions

Many baseline variables pertaining to acute stroke are collected in LSR and Riksstroke upon inclusion after index stroke and are used as baseline characteristics in papers I-IV. In papers III-IV, outcome data from LSR PopR was also used, using a wide array of outcome measures. In the following section, definitions and methods of ascertainment for both baseline characteristics and follow-up assessments will be clarified.

Baseline Characteristics and Assessments

Stroke Classifications

First-ever stroke was classified into the main pathological subtypes: IS, ICH, SAH and undetermined (UND), as verified through CT and/or MRI imaging of the brain,

or autopsy reports. In SAH, if neuroimaging was negative, a lumbar puncture confirming diagnosis was necessary.

Using participants' medical records, IS cases were classified into clinical syndromes according to the OCSP [93] by two physicians, including the thesis author. Likewise, pathogenetic mechanisms of IS were assessed using both TOAST [43] and CCS [44] by two physicians, including the thesis author.

Stroke severity is routinely assessed with NIHSS in the LSR by NIHSS-certified research nurses via personal examination during the patients' hospital stay or via medical records. Patients that were not included in the LSR or where NIHSS data was missing, medical records were retrospectively reviewed by NIHSS-certified physicians, including the thesis author to assess acute stroke severity [236]. Patients' worst NIHSS score within 72 hours of symptom debut, but before recanalization therapy, was recorded.

Baseline Characteristics

In papers III and IV, multiple baseline characteristics are used as potential predictive variables for survival, recurrence, and functional outcome.

Data on stroke risk factors are routinely collected in LSR and were collected by the thesis author via medical records if they were missing. Hypertension was defined as blood pressure >140/90 mmHg at discharge, or treatment with antihypertensive medication during the last 2 weeks. Diabetes mellitus was defined as having a prior diabetes diagnosis, fasting plasma glucose levels >6.1 mmol/L or non-fasting plasma glucose levels >11 mmol/L. Heart disease was defined as any of the following: ischemic heart disease including myocardial infarction, angina pectoris, prior percutaneous coronary intervention or cardiac bypass surgery; heart failure, prior cardiac surgery for any reason, or cardiac arrythmias including atrial fibrillation. Hypercholesterolemia was defined as a prior diagnosis of hypercholesterolemia, lipid-lowering treatment within the last 2 weeks, total cholesterol blood levels >5 mmol/L or low-density lipoprotein cholesterol blood levels >3 mmol/L.

Medication data were also collected from medical records, both at baseline and upon discharge from the hospital for hospitalized patients, including whether patients routinely used antiplatelet medication (aspirin, ADP receptor inhibitors, adenosine reuptake inhibitors or thromboxane inhibitors) or anticoagulant therapy (direct oral anticoagulants or warfarin) prior to stroke and whether they were prescribed at discharge.

Stroke patients' living arrangements at baseline were also registered, i.e. whether they lived alone or with someone else and whether they lived without professional home care, with in-home care or at a nursing home or care facility. In paper IV,

living with in-home care or in a care facility at baseline was used as a proxy for pre-stroke function. Participants were also asked about their current employment status.

Participants were assessed for pre-stroke cognitive impairment or depression. Pre-stroke cognitive impairment was defined as prior diagnosis of dementia or cognitive impairment in medical records, or ICD-10 diagnosis codes F00-F09, while pre-stroke depression was defined as prior diagnosis of depression in medical records or ICD-10 diagnosis codes F31-F34.

Finally, participants' burden of comorbidities was quantified at baseline using the CCI (score 0-29) from data obtained from patients' medical records.

Follow-up Assessments

Paper III

In paper III, causes of death were evaluated using ICD-10 diagnosis codes from the Swedish Cause of Death Register described above. Underlying causes of death were categorized into (i) cerebrovascular disease (ICD-10: I60–I69); (ii) ischemic heart disease (ICD-10: I20–I25, including patients with cardiac arrest with no other apparent cause); (iii) cancer (ICD-10: C00–D48); (iv) infectious diseases (ICD-10: A00–B99, G00–G09, I38–I39, J09–J22, J85–J86); (v) trauma (ICD-10: S00–T32, V01–X59); and (vi) other causes. If categorization could not be completed using the underlying causes of death in the Swedish Causes of Death Register (for instance if only respiratory insufficiency was given as sole cause of death), data was complemented with information from contributing causes of death and medical records. Cases were then discussed by two of the paper III authors for a consensus decision.

Stroke recurrence in papers III and IV was defined as any new acute focal (or global in the case of subarachnoid hemorrhage) neurological event with no apparent cause other than vascular, lasting for at least 24 h or leading to death that occurred after the initial ictus (including acute worsening of an established non-progressive deficit that was not considered to be caused by edema, brain shift, hemorrhagic transformation, concurrent illness or drug toxicity) [111]. Recurrent SAHs were also registered, despite index SAH being excluded in papers III and IV to study the pattern of all recurrent stroke, as well as to account for changes from baseline in neurological impairments and other outcome assessments that may also be affected by recurrent SAH. Participants were asked at clinical follow-up visits whether they had suspected or been diagnosed with a recurrent stroke, and case validation was performed via medical record review. Uncertain cases were discussed between the authors.

Outcome Measures

Numerous outcome measures were used at clinical follow-up at 3-4 years after stroke in paper IV. They are presented below, stratified by the main type of outcome they measure [138].

Measures of Functioning

National Institutes of Health Stroke Scale (NIHSS)

NIHSS (0-42; 42 = worst neurological impairment) was also performed at clinical follow-up in paper IV as a measure of neurological impairment [94]. NIHSS-certified authors of paper IV performed the assessments and all follow-up NIHSS assessments were performed in-person.

Montreal Cognitive Assessment (MoCA)

MoCA (0-30; 0 = most cognitive impairment) was performed at the 3-4 year follow up as a measure of cognitive impairment. MMSE was performed concurrently and was performed after MoCA in all cases. The Swedish version 7.0 of MoCA was used throughout, including adding an extra point for those with less than 12 years of education [172].

Patient Health Questionnaire (PHQ-9)

PHQ-9 (0-27; 27 = most severe depression) was used as an assessment of post-stroke depression, in a translated Swedish version, that is not specifically validated in a stroke setting in Swedish. The assessment was performed by interview for patients who were followed up solely via telephone but was otherwise self-administered with aid from the interviewer [237].

Fatigue Assessment Scale (FAS)

Fatigue Assessment Scale (0-50; 50 = most fatigue) [145] was assessed via patients' self-reporting through interview in-person or via telephone.

Measures of Activities

Modified Rankin Scale (mRS)

The mRS (0-5; 5 = worst outcome) was used at 3-4-year follow-up to assess activity limitations as well as functional outcome. The mRS was administered by telephone if participants were unable to attend a clinical visit and were solely followed up via telephone [238]. Modified Rankin Scale results were dichotomized into 0-2 and 3-

5, where 0-2 was considered favorable outcome. At baseline, mRS data was not available and living with in-home care or in a care facility was used as a proxy for pre-stroke activities and function.

Barthel Index (BI)

ADL was assessed with BI (0-100; 0 = most dependency in ADL) at follow-up, either via interview in-person or telephone [155, 239].

Measures of Participation

EuroQoL-5D (EQ-5D)

EQ-5D was used as a patient-reported outcome measure of HRQoL [209]. The EQ-5D-3L was used (i.e. 3-level questions over 5 domains) in a Swedish translation, either at in-person interview or via telephone [209]. The EQ-5D visual analogue scale of general health (0-100; 0 = worst health) was also used [209].

Short Form Health Survey (SF-36)

Question one of the SF-36, "In general, would you say your health is excellent, very good, good, fairly good or poor?" was administered in-person or via telephone at 3-4-year follow-up as a patient-reported measure of HRQoL [206]. The 5 responses in the question were treated as an ordinal scale in analyses.

Stroke Impact Scale (SIS)

The SIS was administered at in-person follow up or via mail to assess patient-reported and stroke-specific HRQoL [211], including the visual analogue scale question on stroke recovery (0-100; 0 = worst recovery). However, SIS data are not included in the papers in the present thesis.

Statistical Methods

Statistics in the thesis were calculated using IBM SPSS Statistics for Windows, versions 23 (paper I) and 25 (papers II-IV). Non-parametric tests were preferred. Between-group comparisons were tested with two-tailed chi-square test or Fisher's exact test for categorical variables, and Mann-Whitney U test for ordinal and non-normally distributed continuous variables throughout. The standard alpha level was $p<0.05$ for all statistical comparisons in the thesis.

Paper I

In paper I, age- and sex-standardized stroke incidence rates were calculated. Population statistics were obtained from Statistics Sweden [227]. Incidence rates were presented standardized to the European Standard Population from 2013 [240], and the Swedish population as of December 31, 2015 [227], and were calculated using the direct method. Incidence rates from 2001-2002 [235] were also standardized to the Swedish population in 2015 for comparisons between the two time periods. A Poisson distribution was assumed (probability distribution where the occurrence of one event does not affect the probability that a second event will occur) when calculating 95% confidence intervals (CIs). To compare case-fatality rates between 2001-2002 and 2015-2016, log-rank test was used.

Paper II

The various data sources (LSR PopR, LSR, Riksstroke, NPR) in paper II were compared through simple numerical comparisons. A visualization of the agreement between data sources was made using a proportional Euler diagram that was created in BioVinci version 1.1.5, developed by BioTuring Inc.

Paper III

In paper III, stroke survival and recurrence were assessed with Kaplan-Meier curves, censored at 1095 days (3 years). The log-rank test was used to test univariate between-group differences in survival and recurrence, provided that the assumption of similar censorship rates between groups was met. Cox regression analyses were used to determine associations between baseline variables and survival and recurrence. Uni- and multivariable Cox regression analyses were performed separately using predefined variables. As described below, one set of variables was used for analyzing predictors for total 3-year survival and recurrence; and another set of variables was used for 3-year survival and recurrence among only IS patients.

When analyzing the total cohort – the following variables were included in the Cox regression analysis: age; sex (female as reference); index stroke subtype (IS as reference); CCI; NIHSS at baseline; hypertension (no hypertension as reference); hypercholesterolemia (no hypercholesterolemia as reference); and current smoking at baseline (no current smoking as reference category).

When analyzing only IS cases – variables included in the Cox regression analysis were: age; sex; TOAST classification of index stroke (CE as reference); OCSP classification of index stroke (LACI as reference); CCI; NIHSS; hypertension; hypercholesterolemia; and current smoking at baseline.

Hazard ratios generated from multivariable Cox regression analyses of survival were visualized using Forest plots generated in Microsoft Excel.

To ameliorate the effect of multiple hypothesis testing in multivariable Cox regression analyses, *p*-values were corrected using the Bonferroni method [241], by dividing the alpha level of 0.05 with the number of simultaneous hypotheses being tested in both papers III and IV.

Paper IV

In paper IV, regression analyses were used to assess predictors as well as potentially associated follow-up variables to both 3-4-year functional outcome (mRS and BI) and HRQoL (SF-36).

The mRS was assessed as an ordinal variable [242], as well as SF-36 with 5 possible responses. Barthel Index was assessed as a continuous variable. Thus, ordinal logistic regression was used to determine predictors and associations at follow-up for mRS and SF-36. Meanwhile, multiple linear regression was used to determine predictors and follow-up associations for Barthel Index.

Two pre-specified models were used: i) including baseline variables as potential predictors; and ii) including both baseline and follow-up variables that could be associated with functional outcome and HRQoL.

Model (i) included age at baseline, sex, NIHSS, CCI, living with or without care at baseline (as a proxy for pre-stroke function, "no" as reference), stroke subtype (IS as reference), recurrent stroke between baseline and follow-up ("no" as reference); and hypertension, diabetes mellitus, heart disease, hypercholesterolemia, and active smoking at baseline (all no as reference).

Model (ii) included age at baseline, NIHSS at follow-up, CCI at baseline, living status at baseline, living alone at follow-up, recurrent stroke; post-stroke fatigue at follow-up (FAS), cognitive impairment at follow-up (MoCA), and depression at follow-up (PHQ-9).

Ordinal logistic regression analyses were performed of mRS and SF-36 at follow-up using both models. To ascertain that the assumptions of ordinal logistic regression were met, multicollinearity was tested with tolerance and variance inflation factor statistics, and the assumption of proportional odds was assessed with the test of parallel lines.

Multiple linear regression analysis was used to assess BI at follow-up using the same two models. To test the assumptions of multiple linear regression: i) partial regression and residual plots were viewed to assess linearity; ii) the Durbin-Watson test was used to assess independence of residuals; iii) homoscedasticity (i.e. equal variance across the included variables) was visualized and assessed using residual plots; iv) multicollinearity was assessed with tolerance statistics; and iv) outliers were checked for influence on the overall regression model using leverage values (threshold value = 0.2) and Cook's distance (threshold value = 1).

Ethical Approval

All studies in the thesis were approved by the Regional Ethical Committee in Lund, Sweden. Papers I and II were approved as per the diary number 2016/179, and papers III and IV in diary number 2018/393. Living participants in the studies either provided informed consent or, if unable to do so, their next-of-kin were consulted before inclusion. Participants who were deceased upon detection were assessed for inclusion in the cohort without further notification to their next-of-kin. Participation in the thesis studies involved no direct risks for the included research subjects.

Results

Paper I

In paper I, 413 first-ever stroke patients with index event between March 1, 2015 and February 29, 2016 were detected in the study area. The median age of included patients was 76 years and 189 (46%) were female. IS was the most common main pathological subtype of stroke (n =334; 81%), and among IS cases PACI was the most common clinical syndrome (n=153, 46%), while UND (n=144, 43%) and CE (n=104, 31%) were the most common pathogenetic mechanisms of IS as evaluated with CCS. A clustered bar chart comparison of the proportion of main types of stroke in the paper I cohort and the 2001-2002 cohort that was used for temporal trend comparisons is presented in Figure 10. Baseline cohort characteristics of the two cohorts are presented in Table 6.

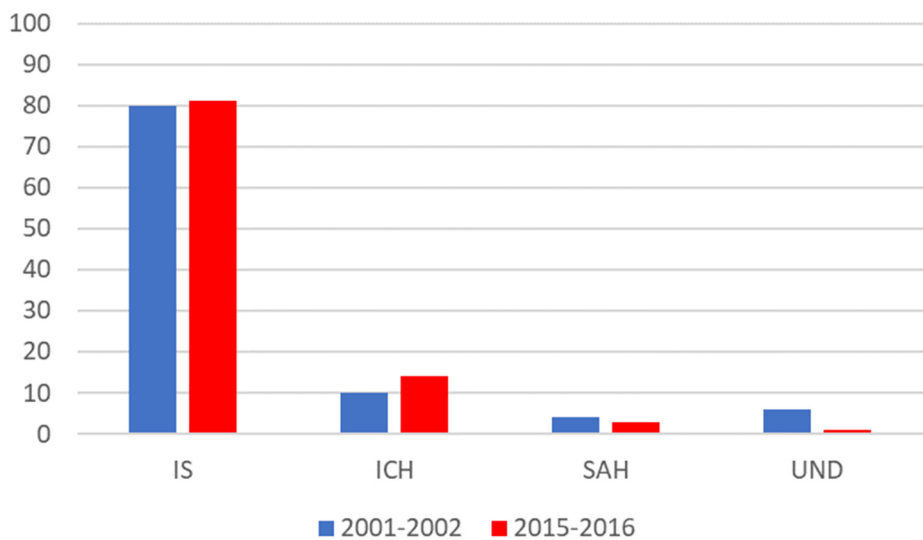

Figure 10. Proportional distribution of main types of stroke in the two compared cohorts in paper I. The y-axis indicates the proportion of the total cohort (%). The total cohort size in 2001-2002 was n=456; and n=413 in 2015-2016. IS: ischemic stroke; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; UND: undetermined main type.

Table 6. Baseline characteristics of first-ever stroke patients in Paper I (2015-2016) and the 2001-2002 cohort used for temporal trend comparisons

VARIABLE	2001-2002	2015-2016	P-VALUE
SEX, FEMALE, N (%)	200 (44)	189 (46)	0.573
AGE, YEARS, MEDIAN (IQR)	76 (67-84)	76 (67-84)	0.808
BASELINE NIHSS, MEDIAN (IQR)	4 (2-10)	5 (2-10)	0.437
SOURCE OF DETECTION, N (%)			0.029
HOSPITAL-BASED REGISTERS (LSR AND/OR RIKSSTROKE)	412 (90)	388 (94)	
PRIMARY CARE & OUTPATIENT REGISTERS	39 (9)	19 (5)	
AUTOPSY REGISTERS	2 (0)	6 (1)	
OTHER METHODS	3 (1)	-	
MAIN TYPE OF STROKE, N (%)			0.001
IS	364 (80)	334 (81)	
ICH	46 (10)	60 (14)	
SAH	17 (4)	14 (3)	
UND	29 (6)	5 (1)	
OCSP CLASSIFICATION, N (%)			0.007
LACI	127 (28)	93 (28)*	
PACI	154 (34)	153 (46)*	
TACI	76 (17)	35 (11)*	
POCI	77 (17)	53 (16)*	
CCS PATHOGENETIC MECHANISM OF IS, N (%)			-
CE	-	104 (31)	
LAA	-	56 (17)	
SAO	-	24 (7)	
OTHER CAUSES	-	7 (2)	
UND-IS	-	144 (43)	

LSR: Lund Stroke Register; IS, ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; OCSP, Oxfordshire Community Stroke Project; LACS, lacunar syndrome; PACS, partial anterior circulation syndrome; TACS, total anterior circulation syndrome; POCS, posterior circulation syndrome; CCS, Causative Classification System for Ischemic Stroke; CE, cardio-aortic embolism; LAA, large artery atherosclerosis; SAO, small artery occlusion; UND-IS, undetermined pathogenetic mechanism of IS. * OCSP classification in 2015-16 only performed for IS cases.

Stroke Incidence

The age- and sex-standardized stroke incidence rate when standardized to the 2013 European Standard Population was 167 (95% CI: 151-184) per 100 000 person-years, and 165 (95% CI: 149-182) per 100 000 person-years when standardized to the Swedish population in 2015. Incidence rates increased with advancing age and were higher among men than women across all ten-year age groups except 75-84

years. The incidence disparity between sexes was more pronounced among IS, where the age-adjusted (to the 2013 European Standard Population) was 107 per 100 000 person-years among women and 165 per 100 000 person-years among men, than among hemorrhagic stroke. Age- and sex-adjusted incidence rates among women and men in 2015-2016, as well as prior data from 2001-2002 for comparison, are presented in Figure 11.

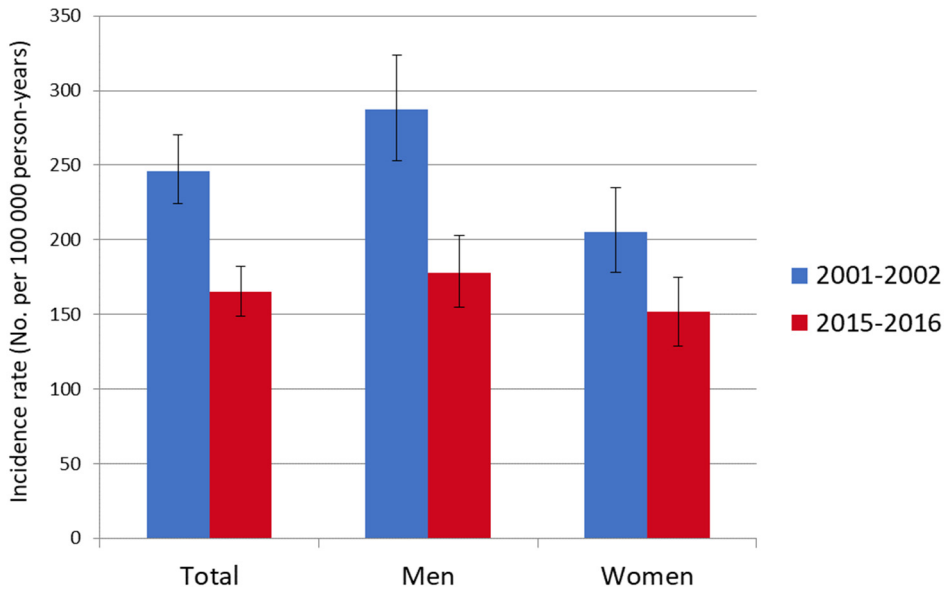

Figure 11. Incidence rates of first-ever stroke per 100 000 person-years among men and women in the catchment area of SUS Lund over two time periods. Incidence rates are adjusted to the Swedish population as of December 31, 2015. Error bars represent 95% CI assuming the Poisson distribution. Image reprinted with permission from Neuroepidemiology, Vol. 50 Aked et al., Temporal Trends of Stroke Epidemiology in Southern Sweden: A Population-Based Study on Stroke Incidence and Early Case-Fatality, pp. 174-182.

Temporal Trends in Stroke Incidence

The total age- and sex-standardized incidence of first-ever stroke decreased 33% between 2001-2002 and 2015-2016 from 246 (95% CI: 224-270) to 165 (95% CI: 149-182) per 100 000 person-years (standardized to the Swedish population in December 2015). Between the two time periods, stroke incidence rates decreased significantly among those older than 65 years from 1077 (95% CI: 968-1195) to 666 (95% CI:596-742) per 100 000 person-years, but no significant decrease was noted among the younger population. Meanwhile, incidence rates decreased for IS from 197 (95% CI: 177-218) to 134 (95% CI: 120-149) per 100 000 person-years, but not for ICH or SAH. Comparisons of first-ever stroke incidence rates between the two

time periods stratified by age and stroke subtype are shown in Figures 12 and 13, respectively.

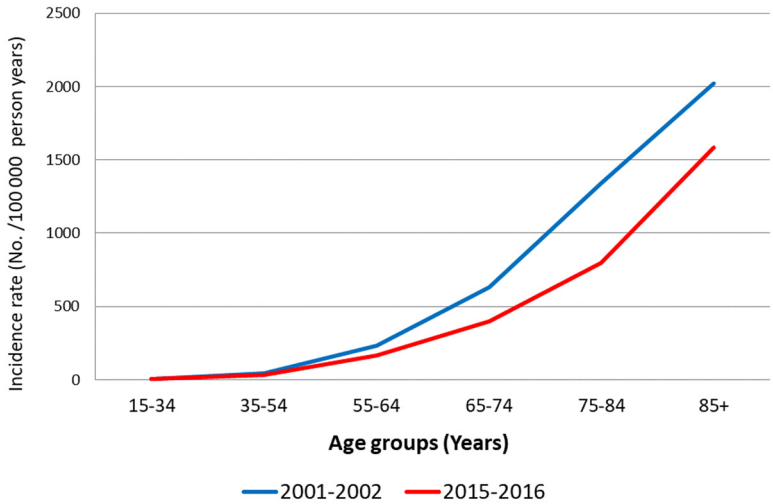

Figure 12. First-ever stroke incidence rates over two time periods across age groups in the catchment area of SUS Lund. Image reprinted with permission from Neuroepidemiology, Vol. 50 Aked et al., Temporal Trends of Stroke Epidemiology in Southern Sweden: A Population-Based Study on Stroke Incidence and Early Case-Fatality, pp. 174-182

Alongside the decrease in stroke incidence from 2001-2002 to 2015-2016, the absolute number of stroke cases in our study area also decreased with 10% from 456 to 413.

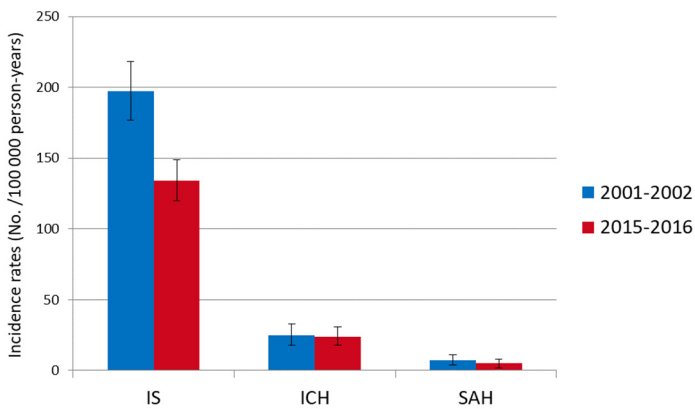

Figure 13. First-ever stroke incidence rates over two time periods among pathological stroke subtypes. Error bars represent 95% CI assuming the Poisson distribution. Image reprinted with permission from Neuroepidemiology, Vol. 50 Aked et al., Temporal Trends of Stroke Epidemiology in Southern Sweden: A Population-Based Study on Stroke Incidence and Early Case-Fatality, pp. 174-182.

Early case-fatality

The 28-day case-fatality of first-ever stroke (all main types) was 11% in 2015-2016. ICH had the highest 28-day case fatality (23%), followed by IS (9%) and SAH (0%). In 2001-2002, 28-day case-fatality was 14%, and there was no significant difference between the two time periods (p=0.165; log-rank test).

Paper II

The same population-based cohort was used in paper II as in paper I, but additional screening of the NPR yielded one extra first-ever ischemic stroke case in our study area and period that had previously been undetected. Thus, the total number of participants in the cohort was 414, and 400 when excluding SAH (n=14).

Case Ascertainment in LSR and Riksstroke

In all, LSR included 363 (91%) of 400 stroke patients (IS and ICH) in the population-based cohort, while Riksstroke included 328 (82%). In total, 375 of 400 (94%) stroke patients in the population-based cohort were detected through LSR and/or Riksstroke, and 24 (6%) additional patients were only detected through retrospective screening of primary care centers (n=11), outpatient clinics (n=7), autopsy registers (n=6), and NPR (n=1).

LSR and Riksstroke overlapped in 316 (84%) cases. Riksstroke detected 12 (3%) cases that were not included in LSR; while LSR detected 47 (13%) cases that were not included in Riksstroke. Out of the 12 patients that were detected by Riksstroke that were not included in LSR, 8 had declined participation in LSR. Those detected by Riksstroke but not included in LSR (n=12) were older than other Riksstroke-detected patients (median 86 vs 76 years; p=0.07) and had higher early case-fatality (42% vs 11%; p<0.01). Conversely, those detected by LSR but not by Riksstroke (n=47) had lower initial neurological impairment (median NIHSS 3 vs 5; p<0.01), lower early case-fatality (0% vs 9%; p=0.02) and were less often hospitalized for their index stroke (83% vs 99% p<0.01).

Early case fatality across the various sources of detection is presented in Figure 14. The overlap between LSR and Riksstroke, as well as sources of detection for other stroke patients are visualized in a proportional Euler diagram in Figure 15.

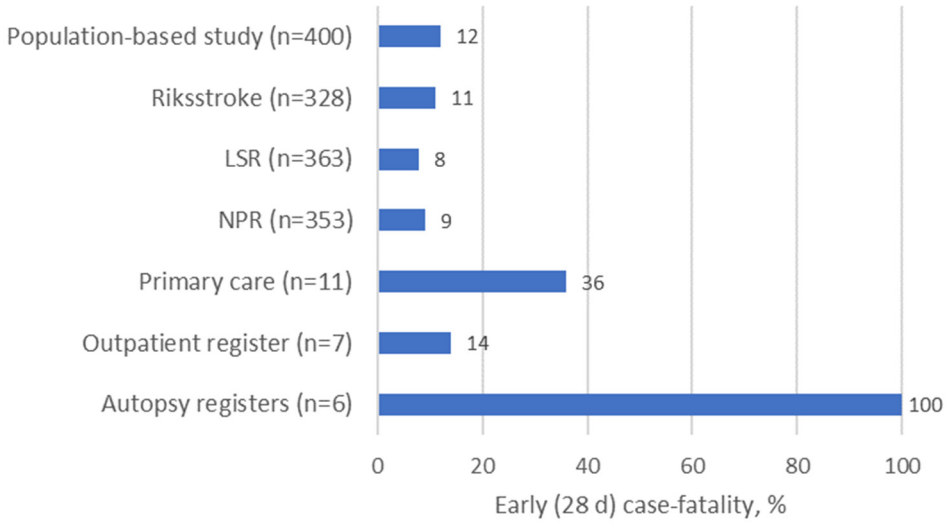

Figure 14. Early (28-day) case-fatality among patients detected by the various sources of case ascertainment in the population-based cohort.

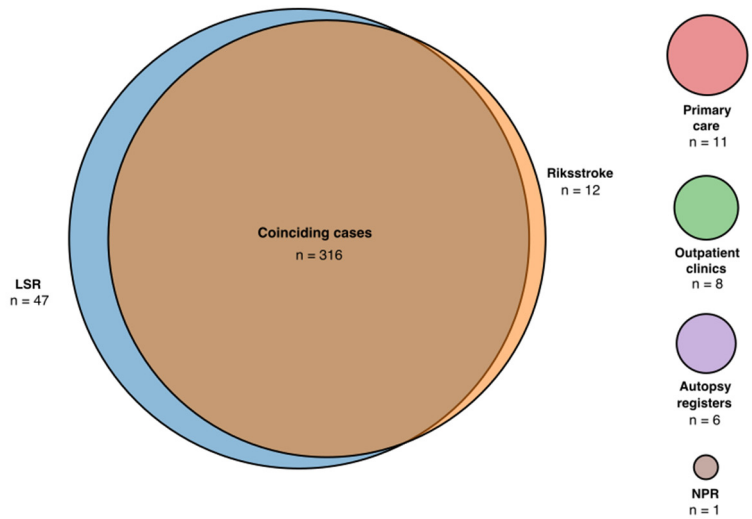

Figure 15. Proportional Euler diagram showing overlap and differences in case ascertainment between LSR and Riksstroke, and other population-based sources. The area of the colored sections represent the number of cases. Total n = 400 cases. LSR: Lund Stroke Register; NPR: National Patient Register. Image reprinted with permission from Acta Neurologica Scandinavica, Vol. 141. Aked et al., Completeness of case ascertainment in Swedish hospital-based stroke registers, pp. 148-155.

When compared to the NPR, a comprehensive in-patient database – LSR detected 336 (95%) of 353 cases in NPR, while Riksstroke detected 315 (89%). Overlap and discrepancies between NPR, LSR and Riksstroke are presented in Figure 16.

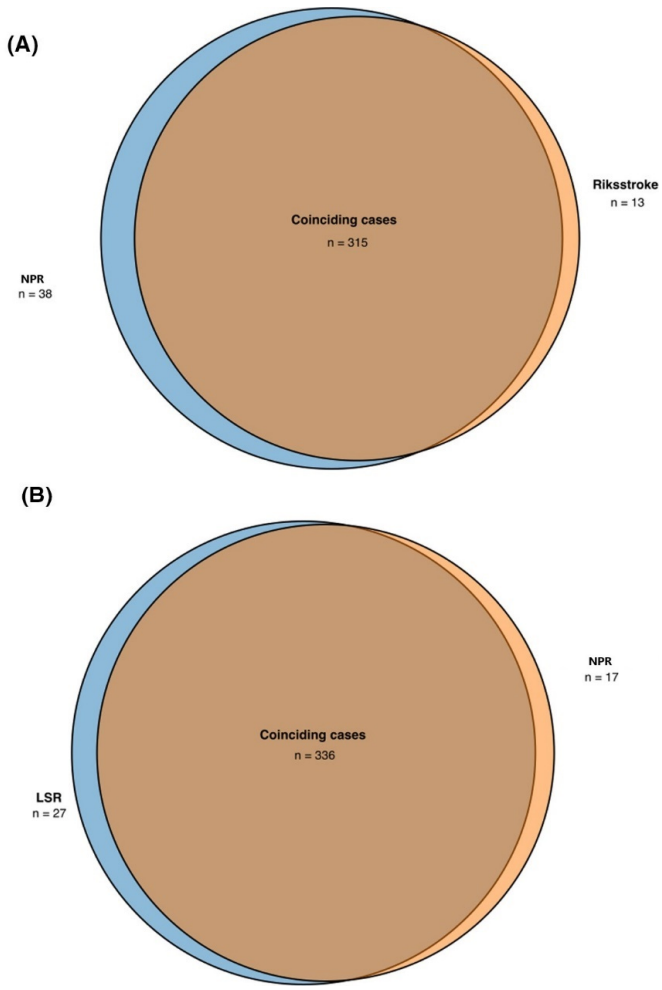

Figure 16. Overlap and discrepancies in case ascertainment between A) NPR and Riksstroke; and B) NPR and LSR. NPR = Swedish National Patient Register. The area of the colored sections represent the number of cases Image reprinted with permission from Acta Neurologica Scandinavica, Vol. 141. Aked et al., Completeness of case ascertainment in Swedish hospital-based stroke registers, pp. 148-155.

Hospital-based vs. Other Sources of Detection

Among the 25 first-ever stroke patients that were neither detected by LSR nor Riksstroke, 28-day case fatality was higher (44% vs 9%; $p<0.001$) than among the 375 patients included in either hospital-based register. Six of the 25 patients were detected via autopsy registers and were deceased upon detection.

Stroke patients who were not detected by Riksstroke (n=72) had less severe neurological impairment at baseline than those included in Riksstroke (n=328) (median NIHSS 3 vs. 5; *p*=0.013). Conversely, stroke patients that were not detected by LSR (n=36) tended to have more severe neurological impairment at baseline than those included in LSR (n=363) (median NIHSS 7 vs 4; *p*=0.068).

Stroke patients that were only detected in primary care databases (n=11) more often lived in nursing homes or other care facilities than those detected by LSR and Riksstroke (57% vs 7%; *p*=0.001).

Finally, 9 patients visited the Emergency Department at SUS Lund and were diagnosed with stroke but not hospitalized in our study period. Of these 9 patients, all were detected by LSR, whereas Riksstroke detected 1 of 9 (11%).

Paper III

In paper III, the same population-based cohort (n=400), excluding SAH, was followed-up at 3 years regarding survival, recurrence and causes of death. All 400 participants were followed up regarding survival status and causes of death. However, 4 (1%) patients were not screened for recurrent stroke due to non-consent for medical record review. Pathogenetic mechanisms of ischemic stroke were assessed with TOAST instead of CCS in paper III, and updated baseline characteristics (including all 400 patients in the final population-based cohort) are shown in Table 7.

Table 7. Baseline characteristics of the paper III cohort, including comparisons between 3-year stroke survivors and those deceased within 3 years

	TOTAL (N=400)	**3-YEAR STROKE SURVIVORS (N=265)**	**DECEASED WITHIN 3 YEARS (N=135)**	***P***
SEX, FEMALE (%)	180 (45)	107 (40)	73 (54)	0.01
AGE, MEDIAN (IQR)	76 (68-84)	72 (65-80)	83 (75-90)	<0.01
CHARLSON COMORBIDITY INDEX, MEDIAN (IQR)	1 (0-2)	1 (0-2)	2 (1-3)	<0.01
NIHSS, BASELINE (IQR)	5 (2-10)	3 (2-8)	8 (4-15)	<0.01
MAIN TYPE OF STROKE, N (%)				0.055
IS	335 (84)	230 (87)	105 (78)	
ICH	60 (15)	33 (13)	27 (20)	
UND	5 (1)	0 (0)	3 (2)	
OCSP CLASSIFICATION (ONLY IS), **N (%)**				<0.01
LACI	92 (28)	75 (33)	17 (16)	
PACI	155 (46)	101 (44)	54 (51)	
TACI	35 (10)	17 (7)	18 (17)	
POCI	53 (16)	37 (16)	16 (15)	
TOAST CLASSIFICATION (ONLY IS), **N (%)**				<0.01
CE	91 (27)	51 (22)	40 (38)	
LAA	44 (13)	35 (15)	9 (9)	
SAO	40 (12)	35 (15)	5 (5)	
OTHER	7 (2)	7 (3)	0 (0)	
UND	153 (46)	102 (44)	51 (49)	

IS: ischemic stroke; ICH: intracerebral hemorrhage; UND: undetermined; LACI: lacunar stroke infarct; PACI: partial anterior circulation infarct; TACI: total anterior circulation infarct; POCI: posterior circulation infarct; CE: cardio-aortic embolism; LAA: large artery atherosclerosis; SAO: small artery occlusion.

3-year Survival

At 3 years after index stroke, 135 (34%) of 400 participants had died. Survival rates were lower among those with index ICH than those with IS (55% vs. 69%; log-rank test p=0.01).

Among all 400 stroke patients, higher age (HR: 1.09; 95% CI: 1.06-1.11); comorbidity burden (CCI; HR: 1.36; 95% CI: 1.22-1.53) and initial level of neurological impairment (NIHSS; HR: 1.11; 95% CI: 1.08-1.13) at baseline were independently associated with worse 3-year survival (at Bonferroni-adjusted alpha level 0.007).

Among those with index IS (n=335), no patients with the pathogenetic mechanism (TOAST) other causes (n=7) died within 3 years. Index CE ischemic stroke had lower 3-year survival (51/91; 56%), compared with both LAA (35/44; 80%); and SAO (35/40; 88%) (log-rank test p=0.01 and p=0.001, respectively). Regarding index clinical ischemic stroke syndrome (OCSP), PACI (HR: 2.81; 95% CI: 1.46-5.41) and POCI (HR: 4.66; 95% CI: 2.12-10.27) were both associated with worse 3-year survival than LACI. There was no significant survival difference between LACI and TACI, but patients with TACI at baseline received acute recanalization therapy in 36% of cases, compared to 9-15% of those with PACI, LACI or POCI (p=0.008). Meanwhile, higher age, comorbidity burden and level of initial neurological impairment were all also independently associated with 3-year survival in the IS subgroup (p<0.005).

Kaplan-Meier curves of cumulative 3-year survival, censored at 1095 days, are presented in Figures 17 and 18, stratified by stroke main type and ischemic stroke pathogenetic mechanism respectively. Forest plots showing the results of regression analyses of potential predictors for 3-year survival among all stroke patients and among index IS patients are presented in Figures 19 and 20.

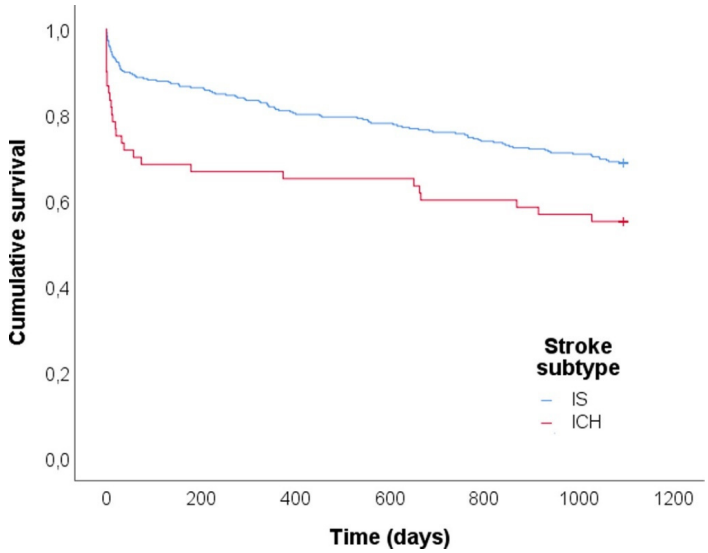

Figure 17. Kaplan-Meier curve of cumulative 3-year survival stratified by stroke subtype in a population-based cohort with total n=400. IS: schemic stroke; ICH: intracerebral hemorrhage. UND (n=5) excluded from analysis due to small number of cases. Image reprinted with permission from European Journal of Neurology, Aked et al., Survival, causes of death and recurrence up to 3 years after stroke: A population-based study, [Epub ahead of print] doi: https://doi.org/10.1111/ene.15041. Copyright (2021) with permission from John Wiley and Sons.

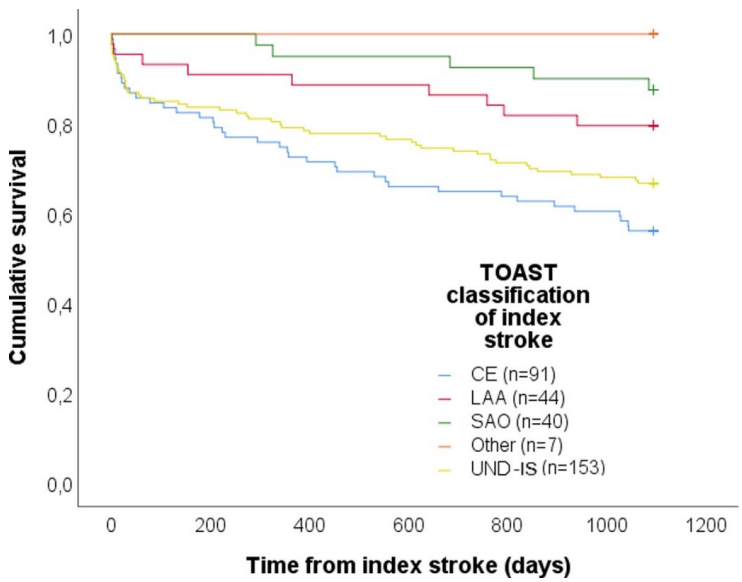

Figure 18. Kaplan.-Meier curves of cumulative 3-year survival stratified by pathogenetic mechanism of ischemic stroke (TOAST) with total n=335. CE: cardio-aortic embolism; LAA: large artery atherosclerosis; SAO: small artery occlusion; UND-IS: undetermined pathogenetic mechanism of ischemic stroke. Image reprinted with permission from European Journal of Neurology, Aked et al., Survival, causes of death and recurrence up to 3 years after stroke: A population-based study, [Epub ahead of print] doi: https://doi.org/10.1111/ene.15041. Copyright (2021) with permission from John Wiley and Sons.

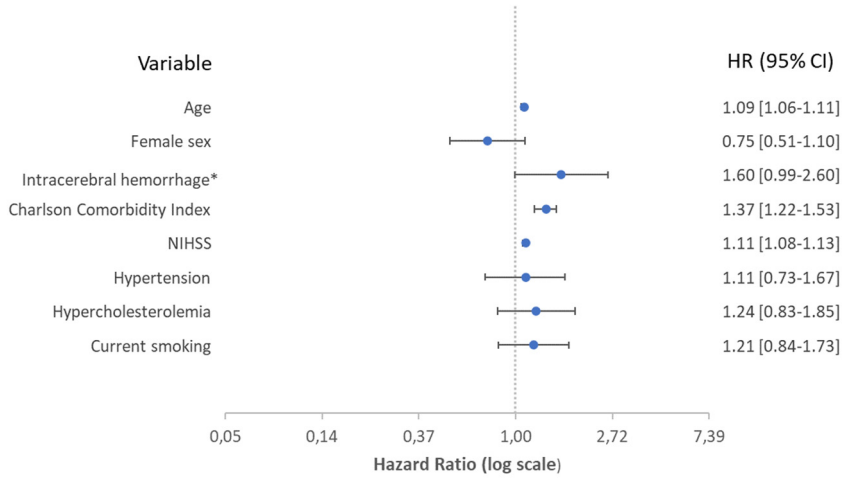

Figure 19. Forest plot visualizing hazard ratios from multiple regression analysis of potential predictors of 3-year mortality among 400 IS and ICH patients. Values to the left of the dotted line are negative hazard ratios and mean a lower risk of death within 3 years. For all dichotomous variables, "no" is reference category. HR: hazard ratio; CI: confidence interval. * as compared to IS.

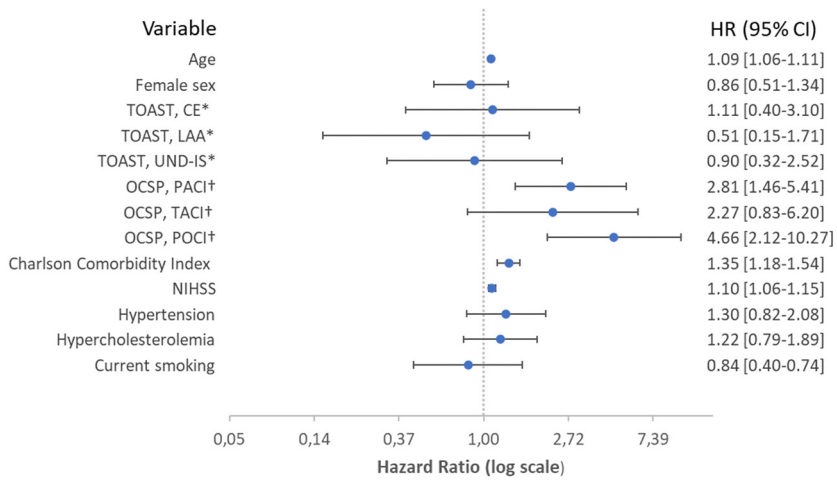

Figure 20. Forest plot visualizing hazard ratios from multiple regression analysis of potential predictors of 3-year mortality among 400 IS and ICH patients. Values to the left of the dotted line are negative hazard ratios and mean a lower risk of death within 3 years. TOAST: Trial of ORG 10172 in acute stroke treatment; CE: cardio-aortic embolism; LAA: large artery atherosclerosis; UND-IS: undetermined pathogenetic mechanism; OCSP: Oxfordshire Community Stroke Project; PACI: partial anterior circulation infarct; TACI: total anterior circulation infarct; POCI: posterior circulation infarct; CCI: Charlson Comorbidity Index. * TOAST, small artery occlusion as reference category; other causes were excluded due to small number of cases leading to extreme CI. † OCSP: lacunar infarct as reference category.

Causes of Death

Among the 135 participants who had died at 3-year follow-up, cerebrovascular disease (54/135; 40%) was the most common cause of death, followed by other causes (34/135; 25%) and ischemic heart disease (25/135; 19%). Other causes included deaths due to cardiac arrythmias, acute vascular pathology and kidney failure. Fifty participants (37%) died due to the index stroke, while 4 (3%) died due to recurrent stroke (two recurrent IS and two recurrent ICH).

In total, 54 (14%) of 400 participants died due to cerebrovascular causes within 3 years, whereas 79 (20%) died of any cardiovascular cause, including both cerebrovascular and ischemic heart disease. Causes of death over time are visualized in Figure 21.

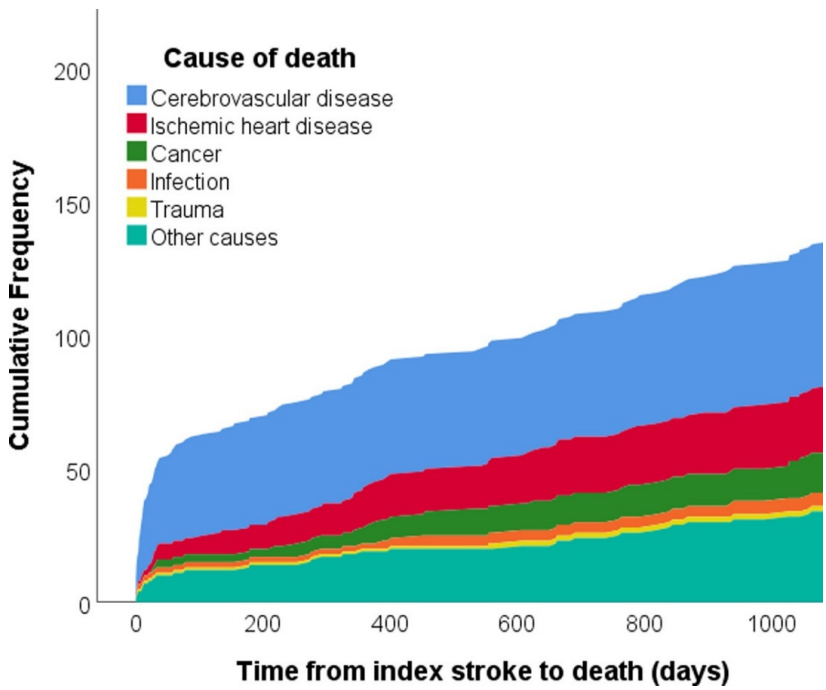

Figure 21. Cumulative frequencies of causes of death within 3 years (1095 days) after first-ever stroke among 400 participants. Image reprinted with permission from European Journal of Neurology, Aked et al., Survival, causes of death and recurrence up to 3 years after stroke: A population-based study, [Epub ahead of print] doi: https://doi.org/10.1111/ene.15041. Copyright (2021) with permission from John Wiley and Sons.

Stroke Recurrence

In total, 30 (8%) of 400 participants had a recurrent stroke within 3 years. Among the 335 participants with IS as index stroke subtype, 29 (9%) had recurrent stroke. Four stroke recurrences were fatal.

Among IS patients that had a recurrent stroke within 3 years (n=29), UND-IS was the most common index pathogenetic mechanism (15/29; 52%), followed by CE (8/29; 28%), and SAO (4/29; 14%). Among those with index IS due to other causes, no stroke recurrence was recorded.

The pathogenetic mechanisms of recurrent IS were the same as the index stroke in 13/29 (45%) cases. Another 13/29 (45%) cases involved a different ischemic pathogenetic mechanism upon recurrent stroke than the index stroke mechanism. Meanwhile, in 3 cases (10%), a recurrent hemorrhagic stroke occurred.

In total (n=30), the most common combination of baseline and recurrent stroke mechanisms or subtypes was UND-IS at both baseline and upon recurrence (6/30; 20%), followed by CE at baseline and recurrence (4/30; 13%), whereas the most common change in mechanisms or subtypes was from UND-IS to CE (4/30; 13%). Finally, only one recurrent stroke occurred among those with ICH (1/60; 2%) at baseline, a recurrent IS with CE pathogenetic mechanism.

Patterns of 3-year stroke recurrence among those with baseline IS are shown in Table 8.

Table 8. Patterns of recurrent stroke within 3 years after of index ischemic stroke, by pathogenetic mechanism of stroke (TOAST)

	ALL INDEX IS (N=335)	INDEX CE (N=91)	INDEX LAA (N=44)	INDEX SAO (N=40)	INDEX UND (N=153)
ANY RECURRENT STROKE, N (%)	29 (9)	8 (9)	2 (5)	4 (10)	15 (10)
RECURRENT CE, N (%)	8 (28)	4 (50)	0	0	4 (27)
RECURRENT LAA, N (%)	4 (14)	0	2 (100)	0	2 (13)
RECURRENT SAO, N (%)	3 (10)	0	0	1 (25)	2 (13)
RECURRENT UND, N (%)	10 (34)	3 (38)	0	1 (25)	6 (40)
RECURRENT HS*, N (%)	4 (14)	1 (13)	0	2 (50)	1 (7)

IS: ischemic stroke; CE: cardio-aortic embolism; LAA: large artery atherosclerosis; SAO: small artery occlusion; UND: undetermined pathogenetic mechanism of ischemic stroke; ICH: intracerebral hemorrhage; HS: any hemorrhagic stroke (ICH or subarachnoid hemorrhage)

Survival Comparisons with Earlier Time Periods

Three-year stroke survival increased continually over the 4 time periods 1983-1985, 1993-1995, 2001-2002, and 2015-2016 (pooled log-rank test, p=0.002). Survival rates were 56% in the first time period, followed by 60%, 64% and then 66% in the paper III cohort. However, there was no significant difference between solely 2001-2002 and 2015-2016 survival rates (pairwise log-rank test, p=0.48). Kaplan-Meier curves of all 4 periods are shown in Figure 22.

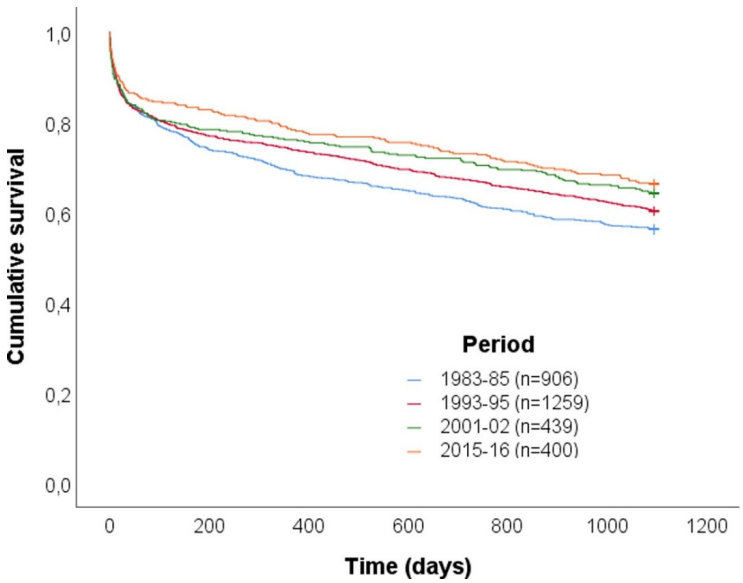

Figure 22. Kaplan-Meier curves of population-based 3-year stroke survival over 4 time periods in our study area. Data from 1983-1985, 1993-1995, and 2001-2002 are adapted from previous studies [228, 229, 235]. Subarachnoid hemorrhage cases were excluded from all data sets. Image reprinted with permission from European Journal of Neurology, Aked et al., Survival, causes of death and recurrence up to 3 years after stroke: A population-based study, [Epub ahead of print] doi: https://doi.org/10.1111/ene.15041. Copyright (2021) with permission from John Wiley and Sons.

Paper IV

In paper IV, the same population-based cohort of IS and ICH as in paper III (n=400) was invited to clinical follow-up at 3-4 years post-stroke.

Loss to Follow-up

In all, 151 of 400 (38%) participants died within 4 years, before attending clinical follow-up. After a median 3.2 years (IQR 3.1-3.5), 202 (51%) participants were followed up in-person or via telephone. Forty-seven (12%) individuals survived 4 years after first-ever stroke but were lost to follow-up. A flow-chart of follow-up

procedure and reasons for loss to follow-up are presented in Figure 23, Baseline characteristics of stroke survivors that were followed up as well as those lost to follow-up are presented in Table 9.

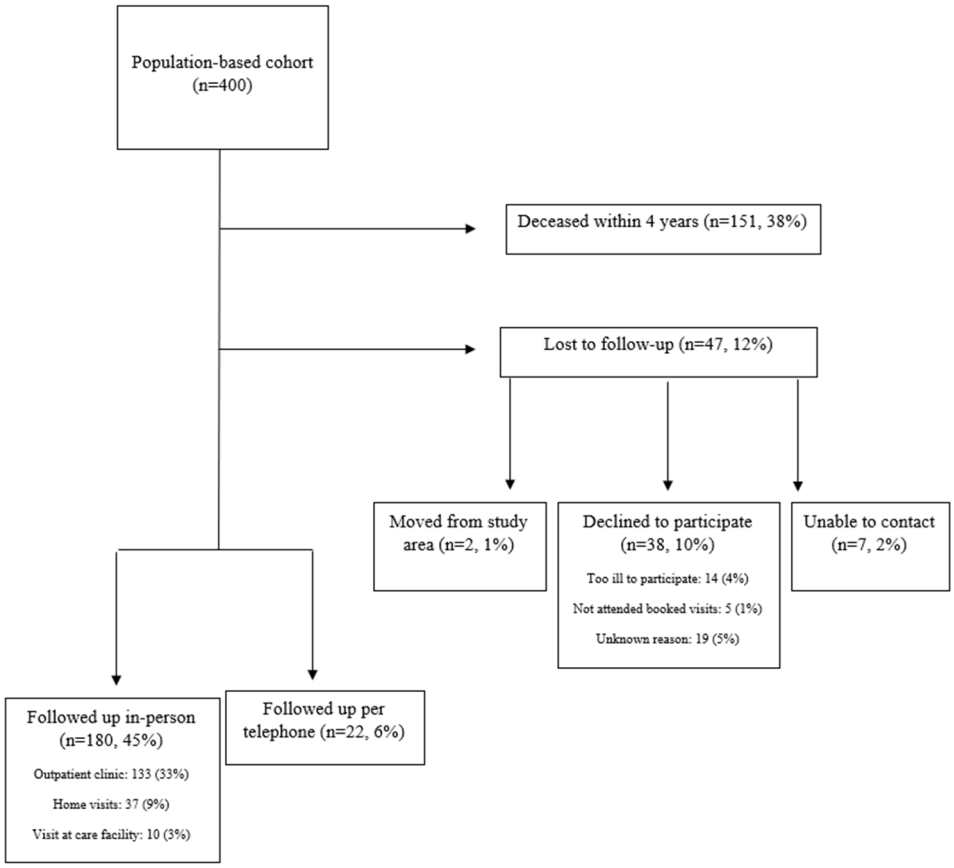

Figure 23. Flowchart of 3-4 follow-up procedure among 400 first-ever stroke patients in paper IV.

Table 9. Baseline characteristics of 3–4-year stroke survivors that attended clinical follow-up and those lost-to-follow-up

	STROKE SURVIVORS FOLLOWED UP AT 3-4 YEARS (N=202)	STROKE SURVIVORS LOST TO FOLLOW-UP (N=47)	*P**
SEX, FEMALE N (%)	80 (40)	19 (40)	1.00
AGE, MEDIAN (IQR)	72 (65-79)	72 (60-86)	0.78
NIHSS AT ADMISSION, MEDIAN (IQR)	3 (2-8)	4 (2-6)	0.95
CHARLSON COMORBIDITY INDEX, MEDIAN (IQR)	0 (0-2)	0 (0-1)	0.61
PRE-STROKE DEPRESSION, N (%)	23 (11)	7 (15)	0.31
PRE-STROKE COGNITIVE IMPAIRMENT, N (%)	8 (4)	7 (15)	<0.01
LIVING SITUATION AT BASELINE, N (%)			<0.01
OWN HOME W/O HOME CARE	185 (92)	34 (72)	
OWN HOME WITH HOME CARE	13 (6)	9 (19)	
ASSISTED LIVING/NURSING HOME	4 (2)	4 (9)	
STROKE MAIN TYPE			0.18
IS	178 (88)	37 (79)	
ICH	23 (11)	9 (19)	
UND	1 (1)	1 (2)	

IS: ischemic stroke; ICH: intracerebral hemorrhage; UND: undetermined

Missing Data

Among outcome measures at 3-4-year follow-up, the proportion of missing values was ≥5% for MoCA (14%), PHQ-9 (5%) and NIHSS (11%). Since these primarily were missing due to participants being unable to attend in-person visits, these missing values were considered missing not at random (MNAR), and no attempt to impute data was performed – instead these cases were omitted.

Activity Limitations at 3-4-year Follow-up

At 3-4-year follow-up, 147 of 202 (73%) stroke survivors had favorable functional outcome, defined as mRS 0-2. Meanwhile, 125 (62%) were completely independent (BI = 100) in ADL. Functional outcome (mRS) data was missing for 47 individuals lost to follow-up, and upon calculating best- and worst-case scenarios (i.e. if either all lost to follow-up had favorable or poor functional outcome) – the possible range of favorable functional outcome is between 59-78%.

Similar proportions of stroke survivors with IS or ICH at baseline had favorable functional outcome at 3-4 years (73% vs. 74%; p=0.88). However, upon also including those who died within 4 years as poor outcome, ICH had a trend towards a lower rate of favorable outcome (43% vs 33%, p=0.22).

Among those with index IS, poor 3-4-year outcome (including death) was most common among the pathogenetic mechanisms CE (32%) and LAA (44%). Those with TACI (15%) as ischemic stroke syndrome at baseline had worst 3-4-year functional outcome (including death), followed by PACI (43%). The distribution of mRS scores in several subgroups of stroke are shown in Figure 24.

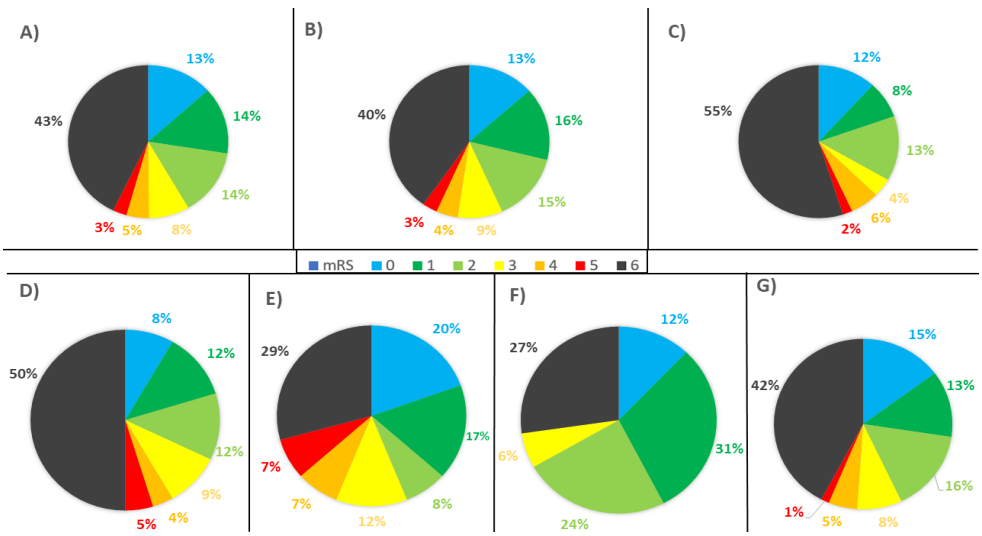

Figure 24. Pie charts showing the distribution of 3-4-year functional outcome (mRS) among followed-up stroke patients in subgroups of stroke**.** mRS 0-6: 0 = no symptoms; 1= no significant disability despite symptoms; 2 = slight disability:; 3 = moderate disability; 4 = moderately severe disability; 5 = severe disability; 6 = death, Participants lost to follow-up are not represented in the diagrams.
A) Total population-based cohort: n= 400; followed-up n=353; lost to follow-up: n=47
B) Ischemic stroke (IS) at baseline: n=335; followed-up n=298; lost to follow-up: n=37
C) Intracerebral hemorrhage at baseline: n=60; followed-up n=51; lost to follow-up: n=9
D) Cardio-aortic embolism*: n=91; followed-up n=84; lost to follow-up: n=7
E) Large-artery atherosclerosis*: n=44; followed-up n=41; lost to follow-up: n=3
F) Small-artery occlusion*: n =40; followed-up n=33; lost to follow-up: n=7
G) Undetermined pathogenetic mechanism*: n=153; followed-up n=135; lost to follow-up: n=18
* Pathogenetic mechanisms of IS according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.

Predictors of Poor Functional Outcome

Ordinal regression analysis of mRS at 3-4 year follow-up of 202 stroke survivors showed that age (HR: 1.03; 95% CI: 1.00-1.05); stroke severity (NIHSS; HR: 1.16; 95% CI 1.10-1.22); living with home care or in nursing facilities (HR: 8.77; 95% CI: 2.98-25.64) and recurrent stroke before follow-up (HR: 3.58; 95% CI: 1.47-8.77) were all independent predictors of worse functional outcome (at $p<0.004$, Bonferroni-adjusted alpha level).

Associations Between Outcome Domains

Ordinal regression analysis using model (ii) (as described on page 55) showed that among 167 stroke survivors who completed all assessments at 3-4-year follow-up: NIHSS at follow-up (HR: 1.59; 95% CI: 1.33-1.89) was independently associated with worse functional outcome (mRS 0-2) at the adjusted alpha level $p<0.006$. Although more post-stroke fatigue, recurrent stroke and decreased cognitive function were associated with worse functional outcome at the alpha level $p<0.05$, these associations were no longer significant after Bonferroni-adjustment to $p<0.006$.

Meanwhile, dependency in ADL (BI) was significantly associated with NIHSS at follow-up (*B*: -3.81; 95% CI: -4.77- -2.85); living with care or in a care facility at baseline (*B*: -18.34; 95% CI: -26.95- -9.73), and post-stroke fatigue at follow-up (*B*: -0.65; 95% CI: -1.05- -0.26) at the adjusted alpha level $p<0.005$.

Full regression results are presented in Tables 10 and 11.

Table 10. Ordinal multivariable regression analysis of associations between follow-up assessments and functional outcome (mRS) at 3-4-year follow-up (n=167)

	HR (95% CI)	*P*
AGE AT BASELINE	0.99 (0.97-1.02)	0.66
SEX, MALE	0.61 (0.32-1.16)	0.32
NIHSS AT FOLLOW-UP	1.59 (1.33-1.89)	<0.001
CCI AT BASELINE	1.31 (1.02-1.69)	0.03
LIVING WITH HOME CARE OR AT NURSING HOME AT BASELINE*	21.74 (5.08-90.90)	<0.001
LIVING ALONE AT FOLLOW-UP	1.48 (0.75-2.89)	0.26
RECURRENT STROKE*	3.05 (1.10-8.47)	0.03
FAS, TOTAL SCORE	1.08 (1.02-1.15)	0.009
MOCA, TOTAL SCORE, INVERSE HR	1.09 (1.01-1.18)	0.03
PHQ-9, TOTAL SCORE	0.96 (0.86-1.08)	0.53

Bonferroni-adjusted p-value = 0.005. * No as reference category

NIHSS: National Institutes of Health Stroke Scale; HR: hazard ratio; CCI: Charlson Comorbidity Index; FAS: Fatigue Assessment Scale; MoCA: Montreal Cognitive Assessment; PHQ-9: Patient Health Questionnaire.

Table 11. Multiple regression analysis of associations between follow-up assessments at 3-4 years and dependency in ADL (n=167)

BARTHEL INDEX, TOTAL SCORE	*B*	95% CI FOR *B*	SE *B*	B	R^2	ΔR^2
MODEL					0.68	0.66
AGE	-0.082	-0.27 - 0.11	0.10	-0.05		
SEX, MALE	-3.69	-8.00 - 0.63	2.18	-0.08		
NIHSS AT FOLLOW-UP	-3.81***	-4.77- -2.85	0.49	-0.53		
CCI AT BASELINE	-2.53**	-4.22 - -0.83	0.86	-0.14		
LIVING WITH CARE AT BASELINE†	-18.34***	-26.95 - -9.74	4.35	-0.21		
LIVING ALONE AT FOLLOW-UP†	0.34	-4.23 – 4.91	2.31	0.01		
RECURRENT STROKE†	-8.15*	-14.92 - -1.39	3.31	-0.12		
FAS, TOTAL SCORE	-0.65***	-1.05 - -0.26	0.20	-0.25		
MOCA, TOTAL SCORE	0.37	-0.13 – 0.88	0.25	0.10		
PHQ-9, TOTAL SCORE	0.78	-0.02 – 1.58	0.40	0.14		

*p<0.05; **p<0.01; ***p<0.005 (Bonferroni-adjusted p-level); † No as reference category
Barthel Index: scale 0-100 where 0 is maximum dependency in ADL and 100 is independence
ADL: activities in daily living; NIHSS: National Institutes of Health Stroke Scale; CCI: Charlson Comorbidity Index; FAS: Fatigue Assessment Scale; MoCA: Montreal Cognitive Assessment; PHQ-9: Patient Health Questionnaire.

HRQoL at 3-4 years Post-stroke

Among 195 stroke survivors who completed SF-36, question 1, 134 (69%) reported good-excellent overall health. Those who reported poor-fair overall health more often had diabetes mellitus at baseline (34% vs. 14%; p=0.001), and higher degrees of neurological impairment (median NIHSS 2 vs. 1; p<0.001), post-stroke fatigue (median FAS: 24 vs. 15; p<0.001), cognitive impairment (median MoCA 23 vs. 25; p<0.001) and depressive symptoms (median PHQ-9 6 vs. 2; p<0.001) at 3-4-year follow-up.

Furthermore, ordinal regression analysis (model (ii) as described on page 55) of SF-36 at follow-up identified post-stroke fatigue as independently associated with worse HRQoL (HR: 1.15; 95% CI: 1.08-1.22; p<0.001).

Finally, among 188 stroke survivors who completed the entire EQ-5D questionnaire, 82 (44%) reported some difficulty or being confined to bed regarding their mobility; 39 (21%) reported some difficulty or being unable to manage their self-care, and 61 (32%) reported some difficulty or being unable to partake in their usual activities. The median self-reported overall health on EQ-5D's visual analogue scale (n=194) was 72/100 (IQR: 50-88). Proportions of EQ-5D responses are presented in Figure 25 and the distribution of SF-36 responses among stroke survivors in various subgroups are presented in Figure 26.

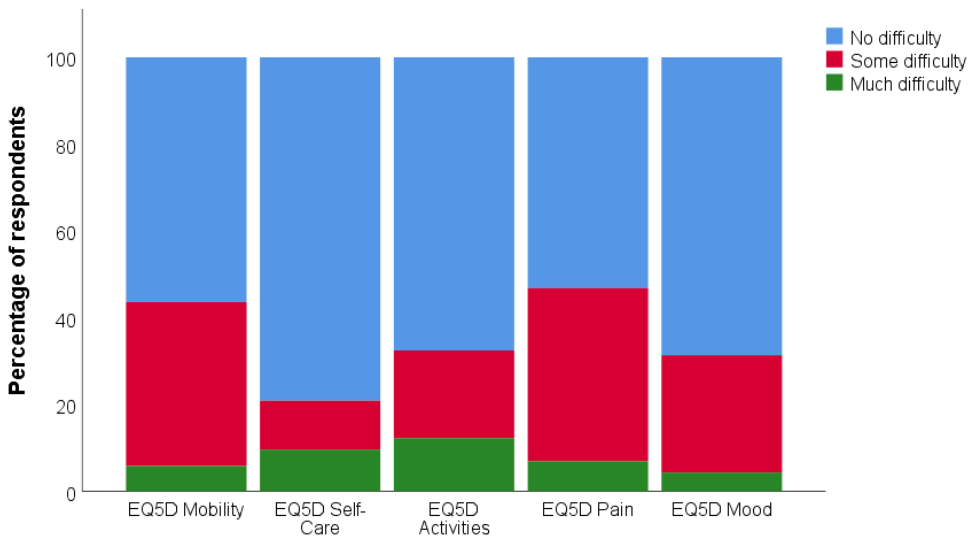

Figure 25. Responses to EQ-5D domains among 188 stroke survivors at 3-4-year follow-up

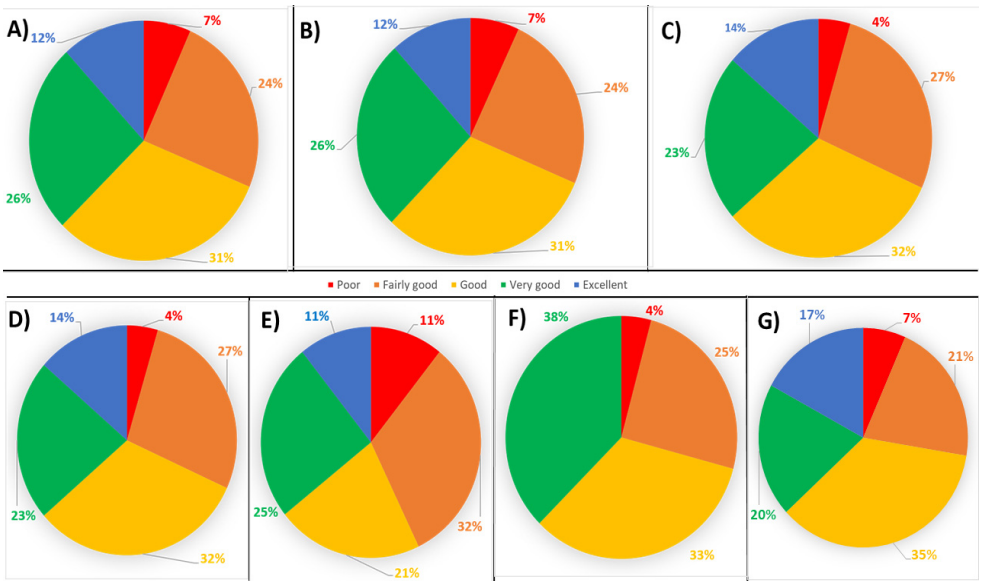

Figure 26. Pie charts showing the distribution of 3-4-year health-related quality of life (SF-36, question 1) among the responding stroke survivors in various subgroups .
Patients deceased within 4 years prior to follow-up and patient lost-to-follow-up are not represented in the diagrams.
A) Total population-based cohort: n=400: 195 respondents, 151 deceased within 4 years, 54 lost-to-follow-up/missing
B) Ischemic stroke (IS) at baseline: n=335: 172 respondents, 120 deceased within 4 years, 43 lost to follow-up/missing
C) Intracerebral hemorrhage at baseline: n=60: 22 respondents, 28 deceased within 4 years, 10 lost-to follow-up/missing
D) Cardio-aortic embolism*: n=91: 39 respondents, 42 deceased within 4 years, 10 lost-to-follow-up/missing
E) Large-artery atherosclerosis*: n=44; 28 respondents; 12 deceased within 4 years; 6 lost to follow-up/missing
F) Small-artery occlusion*: n=40; 24 respondents; 9 deceased within 4 years; 7 lost to follow-up/missing
G) Undetermined pathogenetic mechanism*: n=153; 76 respondents; 57 deceased within 4 years; 20 lost to follow-up/missing
* Pathogenetic mechanisms of IS according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.

Discussion

Methodological Considerations

In observational studies, such as the four papers in this thesis, the internal and external validity are important considerations when interpreting results. The internal validity refers to the robustness and validity of inferences and results and considers the methods used to collect, analyze and interpret data. The external validity of a study refers to whether the obtained results are also valid outside of the study population, i.e. the generalizability of the results [243].

Upon selection of the study population, data collection, analysis and interpretation, there are many biases that can be introduced that threaten the validity of the results. Confounding, information bias, selection bias and attrition bias are all relevant methodological biases that may affect the results in this thesis – and are discussed below.

Case Ascertainment and Selection Bias

The population-based cohort assembled in paper I adhered to all basic updated criteria of an optimal stroke incidence study, and some supplementary criteria for advanced studies [34]. Case ascertainment was based on multiple overlapping sources of information and partly prospective in its design regarding LSR and Riksstroke. The study population was reasonably sized and was well-defined due to reliable and continually updated Swedish population statistics and simple data linkage between databases using Swedish personal identification numbers [227, 232].

The comprehensive nature of LSR and Riksstroke for hospital-based stroke, paired with extensive retrospective screening should have led to a relatively complete case ascertainment and minimal risk of selection bias. However, an important caveat in this cohort is that 9 of 27 primary care centers were unable to be screened for possible stroke cases due to regulatory restrictions regarding privately administered primary health care. Among the 18 public primary care centers that were included in the screening process, 1440 individuals' medical records were screened for eligible first-ever stroke. Eleven patients were detected from the screening of

primary care, which gives a case ascertainment rate of 0.8%. In the primary care database, 522 possible stroke cases at private primary care centers were identified. When extrapolating the case ascertainment rate in primary care of 0.8% to the remaining 522 cases to be screened – it can be estimated that 4 additional first-ever stroke patients were missed by the omission of the private primary care centers. However, the actual case ascertainment rate and demographics of potential stroke patients at the 9 private primary care centers is unknown, which could introduce a small amount of selection bias. Our results in paper II show that stroke patients that solely were detected in primary care more often lived in nursing homes or other care facilities at baseline. If the demographics of hypothetically detected stroke patients in private primary care were different, for example if many individuals that lived independently had a stroke in our population and only had contact with a private primary care center, this could have introduced bias. Nonetheless, it is plausible to assume that the difference in stroke case ascertainment and demographics is not extremely dissimilar in public versus private primary care in our area.

Since the goal in a population-based cohort is to include all stroke patients in the entire study population, there was little deliberate selection of patients. The cohort's inclusion and exclusion criteria in paper I aim to include all stroke as per the WHO definition [12] in our study population. Traumatic and iatrogenic stroke, are excluded due to not adhering to the WHO definition [12] since apparent causes other than vascular are present. Since the WHO stroke definition is used and not the updated AHA/ASA definition [16], "silent" strokes are not included either. These patient selections mostly affect the external validity of the results, since our findings cannot be readily generalized to a population including these additional stroke types. However, when considering stroke as defined by the WHO [12], our results are likely representative of our study population.

In papers II-IV, cases of SAH are excluded from comparisons and from analyses of 3-4-year follow-up. The rationale for this selection is that the small amount of included SAH patients (n=14) is too small a sample size to draw any valid conclusions from this subgroup. This selection further narrows the generalizability of our results somewhat, but outcome and case ascertainment data for IS and ICH are not notably affected by sampling or selection bias. However, presented outcome data in papers III and IV is affected by attrition bias as is described in the following section.

Attrition Bias (Loss to Follow-up)

Stroke outcome data in papers III and IV in this thesis were dependent on the participation of individuals in the original thesis cohort. Stroke survivors who could not be reached or who declined participation were considered lost to follow-up, and some elements of their outcome data remain unknown. This creates an opportunity

for bias in the outcome data. If the risk of non-participation for an individual is affected by either the studied outcome itself or by factors that affect the outcome being studied, results may be biased (attrition bias) [243].

In paper III, only 4 patients included at baseline were lost to follow-up regarding stroke recurrence due to non-consent. Since these patients constitute only 1% of the cohort (n=400), it is unlikely that this attrition has had a meaningful effect on stroke recurrence findings, despite the relatively low event rate of stroke recurrence in the cohort.

However, in paper IV, 47 individuals (12%) that survived their index stroke for at least 4 years were lost to follow-up. Upon subgroup analysis of these individuals, they were more likely to have pre-stroke cognitive impairment and/or live with home care or at care facilities at baseline. Pre-stroke dependency, as measured as needing home care or living in care facilities at baseline, was related to poor functional outcome and dependency in ADL among those available for follow-up in our cohort. A higher proportion of the 47 lost-to-follow-up individuals were dependent at baseline than among those followed up. Hence, it is possible that the rates of poor functional outcome and dependency at 3-4 years in our study are underestimated, due to attrition of a subgroup of individuals with a major baseline risk factor for poor outcome.

The attrition rate in our study is comparable with some other long-term outcome studies of stroke, despite being fully population-based and not excluding patients that are unlikely to be able to participate in follow-up – which is sometimes done in cohort studies to reduce attrition bias [141, 143, 163].

To attempt to mitigate attrition bias in paper IV, home visits were available for participants that were not able to attend a visit at the Department of Neurology. Furthermore, the follow-up window was set at 3-4 years, i.e. we attempted to contact and follow-up stroke patients up to 4 years after stroke onset. Patients who died but were not followed up via in-person or telephone assessment within 4 years were considered followed up with death as the clinical outcome. Meanwhile, if a patient was followed up via telephone or in-person visit and subsequently died within 4 years, the earlier endpoint of clinical follow-up was used as outcome and the available interview data was used. This approach somewhat diminishes the precision of the study – since stroke survivors could potentially be a year apart between their index stroke at follow-up. However, the approach yielded less attrition bias, and since all participants were in the chronic phase of stroke in which further substantial recovery is not expected [244], it is unlikely that the stroke survivors' functional outcome drastically changed over the year that follow-up could take place.

Similarly, paper IV had a connected attrition issue regarding missing values for the outcome measures NIHSS, MoCA and PHQ-9. NIHSS and MoCA require in-person assessment and are therefore missing for those followed up only by telephone. Some patients who were followed up in-person did not want to or did not have energy to complete these two outcome measures, that are likely the two most energy-consuming measures for participants. PHQ-9 was administered last in the clinical protocol and could therefore be missing in a higher degree. Missing values can be addressed using imputation, a statistical method of inferring missing information by using data from other participants. This method requires a large sample size with many available variables and responses that can be used to infer the missing information. Moreover, imputation can give misleading results if data are "missing not at random" (MNAR), i.e. data are missing due to a systematic difference between participants with missing data, and participants without missing data [245]. In the case of paper IV, we considered the missing data MNAR due to it being related to the need of telephone interviews rather than in-person interviews, which in turn may be related to functional status. Therefore, no attempt at data imputation was performed in the present study.

Information Bias

Information bias refers to the distortion of research results due to measurement errors or misclassification [243]. Information bias can be differential which refers to when data are systematically worse in some individuals, or non-differential when data errors occur similarly across groups.

Paper I

In paper I, validation of stroke cases was paramount to accurate incidence calculations. The thesis author performed the screening process and unclear cases were discussed within the research group for a consensus decision. Inclusion and exclusion criteria were well defined beforehand. The vast majority (97%) of ischemic stroke cases underwent CT imaging, which also aided decisions on pathological subtype of stroke. A further 1% were diagnosed via clinical autopsy. Meanwhile, study population data from Statistics Sweden [227] is continuously updated and considered to be reliable [227].

Paper II

Paper II included comparisons between LSR and Riksstroke and though decisions on inclusion in the population-based thesis cohort were made by the thesis author and the research group, no assessment was made of inter-observer reliability between LSR and Riksstroke, which may have partly explained the registers' differences in case ascertainment. Different case reviewers might have slightly different interpretations of the available data for inclusion, and an individual case

might, for instance, be excluded upon case review from Riksstroke, but included by the thesis author via inclusion in LSR or another source of detection.

Paper III

Paper III used multiple baseline and outcome measures. Data on stroke risk factors were in part collected by research nurses at LSR according to a clearly defined protocol and validated by the thesis author.

NIHSS assessments at baseline were performed by NIHSS-certified LSR research nurses via medical record review with complementing information from clinical in-hospital assessment where possible.

Similar to case ascertainment in paper I, possible recurrent stroke events were discussed in the research group if there was uncertainty. Furthermore, stroke survivors were also asked at follow-up if they had been diagnosed or suspected a recurrent stroke event, as a separate source of information to improve recurrence data.

Finally, as discussed in the Methods section, cause of death data from death certificates in the Swedish Cause of Death Register have shown high agreement with medical record review [233]. However, the validity has been questioned among the elderly [234]. In paper III, the thesis author categorized the causes of death into pre-defined categories as an attempt to summarize the data . This may be a source of some misclassification due to the need of interpretation of death certificates which could have been inaccurately entered or entered with insufficient detail. Finally, to reduce the risk of misclassification, causes of death were validated via medical records where possible, and cases were discussed in the research group if there were uncertainties. Similar categorizations have previously been used in cause of death studies of stroke [246].

Paper IV

At 3-4-year clinical follow-up, multiple outcome measures were assessed. The two major outcomes were functional outcome as measured with mRS and BI, and HRQoL as measured by EQ-5D and SF-36. Outcome measures were used by one of four physicians (J. Aked, F. Wennerström, M. Stenman, M. Jensen) who performed the follow-up assessments. All 4 physicians were NIHSS-certified and were educated in the administration of the outcome measures before use. The clinical protocol used at follow-up visits included all interview questions for reference and the questions had clearly defined answers without open-ended questions, which also abates the risk of information bias.

The outcome measures used have been previously validated in stroke and had acceptable psychometric properties. The mRS was one major outcome in paper IV and has excellent inter-rater reliability [155]. BI has excellent reliability but suffers

from a significant ceiling effect, which is in itself a form of information bias since it can alter model effects in regression analyses [162, 247]. However, the risk of type 1 error (false positives) was lessened with Bonferroni correction of the alpha level in the linear regression analyses in paper IV. Moreover, the use of ordinal or continuous rather than dichotomized outcome measures in stroke has previously been recommended [248]. In all, the ceiling effect of BI may have introduced information bias in the linear regression analyses in paper IV and caution may be warranted upon interpreting these results.

Similarly, regarding HRQoL, the other major outcome in paper IV; the SF-36 has significant floor and ceiling effects that may also introduce bias [209], while EQ-5D has shown acceptable reliability and validity in stroke [209].

Other outcome measures that were used as independent variables in paper IV to elicit associations between functional outcome, HRQoL and other domains of functioning were all validated in stroke and had adequate psychometric properties. The patient-reported outcome measures (PROMS) that were used also asked questions about the last 2 weeks or the last month, and thus minimized the risk of introducing recall bias – a mechanism of information bias wherein participants have different accuracy in recalling events - that in part depends on how long ago the event in question occurred.

One final source of information bias in paper IV is the lack of a validated and standard measure of pre-stroke function, such as mRS. Instead, living with in-home care or in a care facility was used as a proxy for poor functional outcome, with less well-known psychometric properties.

Confounding

Confounding refers to when a variable is associated with both the measured exposure and the measured outcome [243]. This variable is then called a "confounder" and accounts for some of the relationship observed between the exposure and outcome [243]. Due to this, it can distort estimates of associations between exposure and outcome and elicit spurious associations between variables that are actually explained by the confounder variable. Bias due to confounding can be minimized if the confounders are known and measured. This can be achieved by stratifying data or by multivariate regression adjusting for potential confounders [243].

In paper I, incidence rates were adjusted for age and sex relative to the Swedish population and a European Standard Population. Upon comparisons of incidence rates from different geographical areas, a potential confounder of differences in incidence rates is a simultaneous difference in age or sex distribution between the two populations. The Swedish population in 2015 and the updated European

Standard Population from 2013 were similarly distributed and thus yielded similar age- and sex-standardized incidence rates (165 vs. 167 per 100 000 person-years). Standardization to another population such as the world standard population or the older version of the European standard population would likely produce a lower age- and sex-standardized incidence rate due to a higher proportion of young people in these populations, while stroke primarily occurred among those older than 65 years. To be able to accurately compare incidence rates, it is therefore important to standardize to a common population.

Paper III examined associations between baseline variables and the risk of death within 3-years with multivariable Cox regression analysis. For example, when studying the association between various TOAST subtypes and 3-year survival, age and comorbidities are two variables that could potentially have caused confounding upon not adjusting for them. Both age and burden of comorbidities such as heart disease likely influence both which TOAST subtype is most common and 3-year survival, i.e. both the exposure and outcome, and need to be considered via adjustment when studying the association. In the univariable Cox regression analysis in paper III, CE is an independent risk factor for death within 3 years when compared to SAO, but this effect did not persist when adjusting for other variables such as age and comorbidities in the multivariable model.

Likewise, in paper IV, multiple regression models were used to assess associations between baseline and follow-up variables and functional outcome and HRQoL. Important confounding to consider in paper IV included the possible interplay between fatigue and depression [186, 190], and between depression and cognitive impairment [179, 180]. To study for instance the impact of fatigue on functional outcome post-stroke, depression needs to be considered due to its potential effect on both the prevalence of fatigue and poor functional outcome. Also, as previously described, although we lacked an accurate standard measure of pre-stroke function – we attempted to adjust for this potential confounder using the proxy variable of needing professional care prior to stroke – since pre-stroke function can affect both dependent variables such as depression, as well as functional outcome.

External Validity

External validity refers to the generalizability of results and is primarily dependent on the studied population. The population surrounding SUS Lund examined in the present study is likely similar to populations in other high-income settings. However, data on ethnicity in the study area is not readily available, but since stroke rates have been shown to differ among various ethnic groups [68], results may not be generalizable to non-Caucasian populations. Furthermore, the municipality of Lund has one of the highest rates of higher education among Swedish municipalities and was the largest municipality in the study population [227]. This may have had

an influence primarily on results regarding cognitive impairment after stroke, but the risk of this is partially decreased by the MoCA outcome measure including an adjustment of one extra point for those with less than 12 years of formal education [166, 172].

General Discussion

Stroke Incidence

The major finding in paper I was that the overall incidence of first-ever stroke in our study are decreased by one third between 2001-2002 and 2015-2016. Furthermore, the absolute number of first-ever stroke cases decreased from 456 to 413, by nearly 10%. This decrease occurred despite a population growth of 18% in our study area, and a 1% increase in the proportion of individuals over 75 years of age.

Our finding of decreasing stroke incidence in this high-income setting is in line with other studies from high-income areas [3, 21], and has since been corroborated in a recent meta-analysis [7]. However, in prior studies, the absolute number of strokes has been projected to increase [3, 249].

Stroke incidence decreased in all age groups over 65 years in our study, but not among the younger. Similar tendencies have been reported elsewhere and some studies have even reported increasing stroke incidence among younger individuals since the beginning of the millennium [23, 24]. This may be related to an increased risk of certain stroke risk factors in the younger population [24] but may also in part be explained by the finding of decreasing incidence of ischemic stroke and static incidence rates of hemorrhagic stroke - which is proportionally more common among the younger [250]. Furthermore, the recent advances in stroke prevention therapy may have been targeted primarily at the elderly population. Altogether, these trends warrant heightened surveillance and focus on reducing stroke risk factors and preventing stroke among the young.

Early Case-fatality

In paper I, we found that case fatality rates in our area decreased somewhat but were not significantly different between 2001-2002 and 2015-2016. Similar results of small declines or stable case-fatality were reported from other high-income countries around the same time period [21]. In 2015-2016, mechanical thrombectomy treatment was newly introduced as a primary acute therapeutic option in routine care – and it is possible that early case fatality after stroke has since

been affected by increasing thrombectomy rates. According to Riksstroke data, the absolute number of mechanical thrombectomy procedures in the southern healthcare region (including SUS Lund) has more than doubled from 2015 to 2020 [251]. Although the original trials of mechanical thrombectomy were designed to detect improvements in functional outcome and neurological impairment [96], later meta-analyses have shown 90-day survival benefits of mechanical thrombectomy in acute ischemic stroke [252]. Besides the introduction of mechanical thrombectomy, increased uptake of anticoagulant therapy may have reduced the proportion of cardioembolic IS in the first-ever stroke population, which is associated with the highest mortality rate among ischemic pathogenetic mechanisms [253]. Conversely, this may have contributed to a higher proportion of ICH in 2015-2016 (14%) compared to 2001-2002 (10%), which is associated with high early case fatality and may have slightly diminished the difference in early case fatality between the two periods. This change may similarly have affected ICH incidence over time through an increase in anticoagulant-associated ICH, which might contribute somewhat to the static incidence rate of hemorrhagic stroke described above [251].

Case Ascertainment in Hospital-based Stroke Registers

In paper II, evaluation of hospital-based screening methods in Riksstroke and LSR showed that 10-20% of first-ever stroke cases may go undetected with purely hospital-based case ascertainment. The completeness of case ascertainment in Riksstroke was 82% when compared to the population-based cohort, which is an improvement from 63% in Örebro, Sweden in 1999-2000 [36]. The completeness of LSR was 91%, as in prior studies of LSR from the beginning of the millennium [228]. Riksstroke and LSR have different scopes and therefore different methods for case ascertainment. Whereas LSR prospectively includes patients based on both Department of Neurology inpatients and outpatients, as well as screening Emergency Department patient lists – Riksstroke prospectively includes inpatients at the Department of Neurology and other case ascertainment occurs retrospectively via ICD-10 diagnosis codes. Hence, it is understandable that LSR includes more patients with minor stroke than Riksstroke, considering it also includes screening of outpatients and the Emergency Department. In paper II, the 47 stroke patients who were detected in LSR but not in Riksstroke tended to have less severe strokes, lower early case fatality and were less often hospitalized for stroke.

On the other hand, 12 patients were included in Riksstroke but not in LSR, and 8 of these patients were detected by LSR but not included due to lack of consent. These 12 individuals were elderly with high case-fatality and moderate-severe strokes, which likely constitutes situations where obtaining active consent is difficult.

Consequently, paper II shows that the scope and direction of selection bias in different hospital-based stroke studies may vary based on the screening methods

used. Hospital-based registers and studies are very valuable complements to population-based research since population-based methodology is expensive and time-consuming. Hospital-based studies are considered to reliably reflect epidemiological trends as long as the risk of selection bias is known and that the proportion and characteristics of undetected stroke patients do not change vastly over time. Furthermore, in addition to epidemiological estimates, hospital-based registers and studies can of course be of great value for registering quality of care and for in-hospital clinical studies of stroke.

Stroke Survival and Causes of Death

Prior studies from high-income settings have shown a decline in first-ever stroke mortality over the last decades [27], but the rate of decline has stagnated in some regions [30]. The improvement of prevention treatments such as oral anticoagulants for cardioembolic IS, decreased smoking prevalence and improved treatment of high blood pressure have been suggested as potential contributors to increased stroke survival, alongside improved acute stroke therapy [28, 29, 253].

In paper III, the 3-year survival rate of the population-based cohort was 66%, which is in line with other high-income population-based studies, but slightly higher than 59% that was recently reported by a nationwide hospital-based Swedish study [163, 254]. This difference may be in part due to differences in case ascertainment between the two studies, but also due to regional differences in stroke survival throughout Sweden.

In our study area, survival after first-ever stroke (IS and ICH) increased from 60% in the early 1990s to 65% in the early 2000s, and 66% in the 2010s. However, there was no significant difference between survival rates in 2001-2002 and 2015-2016. Early case-fatality was similar but decreased over the 4 study periods and decreased the least numerically (from 14% to 12%) between 2001-2002 and 2015-2016. This may suggest that the decrease in the improvement rate of stroke survival between these periods is mostly due to a worsened long-term survival. The proportion of first-ever stroke patients over 75 years of age in the 4 cohorts was highest in 2001-2002, at 59%, while in all other time periods the proportion was between 44-46%. An increase in the age of first-ever stroke patients is consequently not a clear reason behind the stagnating rate of survival improvement. Since paper I showed a decrease in stroke incidence in the study area in the same time frame, it can be speculated that a decrease in stroke incidence primarily among otherwise healthy individuals with a smaller burden of comorbidities may adversely affect the improvement rate of stroke survival. However, the burden of comorbidity was low in the population-based stroke cohort (median Charlson Comorbidity Index score: 1), and stroke incidence has primarily decreased among those older than 65 years. These findings encourage further surveillance of temporal trends in stroke survival and

investigation of which factors may cause a possible stagnation in stroke survival improvement over time.

In ischemic stroke, the clinical syndrome TACI has traditionally been associated with the highest degree of morbidity and mortality among clinical IS syndromes [93]. However, in our cohort, TACI was not associated with lower 3-year survival than LACI – likely due to the high proportion of patients with TACI that received acute recanalization therapy (35%) compared to among the other IS syndromes (9-15%). Meanwhile, 3-year survival was lowest among those with CE as the pathogenetic mechanism of first-ever IS with a survival rate of just over 50%. Those with CE were also the oldest and had the highest burden of comorbidities. This may explain why there was no significant survival difference between pathogenetic mechanisms upon correcting for these variables in regression analysis.

Finally, the proportion of mortality due to cardiovascular causes was 57% in our study, which is somewhat lower than a previous estimate of about two thirds in a study from 2001 [31]. There are few other available studies of causes of death after stroke, and direct comparisons are precluded due to the questionable diagnostic accuracy in death certificates, especially among the elderly [234, 255]. The high rate of cardiovascular mortality within 3 years after stroke emphasizes the importance of secondary cardiovascular prevention treatment. In a general sense, this also points to an overall global need of further treatment options and interventions in cardio- and cerebrovascular disease prevention as these are major global causes of death and DALYs [1].

Stroke Recurrence

In our cohort, 8% of the studied individuals had a recurrent stroke within 3 years of the first-ever stroke. Over half of those with IS and recurrent stroke changed pathogenetic mechanism or main type of stroke between first-ever stroke and recurrence, and in most of these cases the pathogenetic mechanism of first-ever IS was undetermined. A recent meta-analysis of recurrent IS identified 3-year recurrence rates ranging between 9% and 37%, in which our estimate of 9% recurrence among IS cases is in the lower range [256]. In paper III, after UND-IS, CE was the most common baseline IS pathogenetic mechanism among those that experienced recurrent stroke within 3 years which is similar to most study findings in the aforementioned recent meta-analysis [256]. However, the relatively high recurrence rate among UND-IS cases emphasizes the need of adequate investigation of pathogenetic mechanisms of first-ever stroke to properly prevent recurrence.

Meanwhile, in a global context, stroke recurrence rates appear to have stagnated over the last 20 years despite recent advancements in stroke treatment [256].

However, recent Swedish data shows that nationwide stroke recurrence rates appear to have continually decreased from 28% in 1995 to 20% in 2020 [257].

In all, the pattern of stroke recurrence in paper III particularly highlights the importance of thorough investigation of pathogenetic mechanisms of first-ever ischemic stroke to allow optimal treatment of risk factors for recurrence.

Functional Outcome after Stroke

In paper IV, 73% of the first-ever stroke survivors had favorable functional outcome at 3-4-year follow-up and a similar proportion self-reported good or excellent health, and a majority were entirely independent in ADL.

A similar population-based study of first-ever stroke patients in 2001-2002 has previously been performed of 10-year outcome in our study area, in which 71% had favorable outcome at follow-up [144]. This could speculatively be interpreted as a worsening of functional outcome among stroke survivors between these two studies– since the long-term prevalence of disability has been shown to increase up to 15 years after stroke, and the loss-to-follow-up in the paper IV likely led to an overestimation of favorable functional outcome [143]. Also, rates of favorable functional outcome in our cohort were slightly lower than in other prior studies from high-income settings at 3-10 years [8, 141, 163]. However, it is difficult to make direct comparisons between studies due to differences in case ascertainment methods, geographical areas, recency, loss-to-follow-up and time to follow-up.

Also, although survival among those with TACI was not significantly worse than other IS stroke syndromes in paper III, functional outcome was markedly worse among those with index TACI. Only 15% of TACI survivors had favorable functional outcome as compared to 51-74% among the other stroke syndromes. As previously discussed in the section on paper III, the change in survival among TACI IS may be an effect of enhanced recanalization therapy. It can further be postulated that increased survival in the TACI subgroup may also have led to a greater number of patients that survived with substantial functional impairment.

Both post-stroke cognitive impairment and fatigue were associated with worse basic ADL as measured with BI. Fatigue has previously been implicated in worse complex ADL, but a negative effect on also basic ADL such as in BI has not been reported [189]. However, the limitations of the linear analysis of BI are described above and these findings need further validation. Nonetheless, since fatigue was also independently associated with worse HRQoL, which highlights the importance of post-stroke fatigue as a source of disability and poor outcome after stroke and the need for further study of this symptom.

Conclusions

- Stroke incidence has declined by 33% in southern Sweden since the beginning of the millennium, as well as a decline in the absolute number of stroke cases. However, the decrease has occurred primarily for ischemic stroke and among the elderly which may indicate a need of improved primary prevention for hemorrhagic stroke and for younger individuals.
- Hospital-based stroke registers may not detect up to 10-20% of first-ever stroke patients, particularly in certain subgroups, such as those with fatal strokes or individuals living in nursing homes. The scope and direction of selection bias may vary among hospital-based registers based on their specific methodology, and regular audits are recommended to ensure that the level of selection bias in a register remains similar over time if the register is to be used for estimating epidemiological trends.
- Survival at 3 years after first-ever stroke has increased over the last decades, but the rate of improvement appears to be slowing down despite recent treatment advancements. Most deaths are due to cardiovascular causes, which highly emphasizes the need of secondary cardiovascular prevention after stroke.
- Recurrence rates are relatively low in the study area, but many of those with recurrent stroke change pathogenetic mechanism from baseline to recurrence, and the index IS pathogenetic mechanism is often undetermined in these cases. This highlights the need of thorough and improved evaluation of mechanisms of stroke to adequately prevent stroke recurrence.
- The vast majority of 3-4-year stroke survivors have favorable functional outcome and good to excellent HRQoL, and most are fully independent in ADL. However, our 3-4-year data on stroke outcome are similar to a prior 10-year follow-up study, which may signify a worsening of post-stroke outcome over time in the study area.
- Post-stroke fatigue is independently associated with both worse basic ADL and HRQoL and may be an important target for future interventions to improve post-stroke outcome.

Future Perspectives

Since stroke is a major worldwide cause of death and disability, and the burden of stroke is projected to increase in the coming decades, it is of utmost importance to evaluate epidemiological trends in stroke as well as to perform thorough studies of post-stroke outcome [1]. These studies are needed to improve and maintain preventive strategies, provide accurate prognostic information and to identify areas of morbidity that can be treated or alleviated.

Detailed studies of stroke incidence may help evaluate which primary prevention strategies are of most value to reduce the future prevalence of stroke, as well as identifying geographical areas and subgroups that may be in need of heightened attention. Future studies of stroke among the young, identification of additional possible specific risk factors and how to detect those in most need of primary prevention treatment are necessary to address the stationary – or in some areas increasing – stroke incidence rates in some populations [23, 24]. Likewise, similar knowledge of hemorrhagic stroke risk factors, primary prevention and acute treatment is required to manage the future burden of stroke, especially since hemorrhagic stroke entails a higher risk of mortality and poor functional outcome, as corroborated in this thesis. Particularly, further study of oral anticoagulant-associated ICH may be warranted as the uptake of anticoagulant therapy increases.

To accommodate the continuous surveillance of epidemiological patterns of stroke, as well as evaluating new treatment methods, risk factor profiles and adherence to clinical guidelines – hospital-based stroke studies are of immense value. However, it is important that these studies are assessed for potential selection bias with audits and comparisons with population-based studies to assure their generalizability and avoid erroneous conclusions. Comparisons with population-based studies to quantify local selection bias in hospital-based studies will also likely facilitate interpretation of studies from different geographical areas and lead to a more complete picture of stroke epidemiology worldwide.

Moreover, detailed knowledge of stroke survival and recurrence is important for stroke clinicians to be able to provide adequate prognostic information to patients, as well as being vital for policymakers assessing the societal effects of stroke. While new therapeutic advances such as acute thrombectomy have positive survival effects for ischemic stroke [104], these can be further improved, and acute therapies for

hemorrhagic stroke are still lacking. Since hemorrhagic stroke incidence is unchanged in the studied region, and entails most mortality and disability among stroke subtypes, this is an area that requires further research efforts to improve prevention and outcomes similarly to ischemic stroke in recent decades. Also, further studies of pathogenetic mechanisms of stroke, for instance via genetic studies [150] may uncover new pathogenetic mechanisms and potential therapeutic targets and help minimize the number of patients in which stroke recurs – especially perhaps among those with undetermined ischemic stroke mechanisms.

Finally, further action to alleviate the often-significant morbidity after stroke are needed. In chronic stroke, there is a lack of treatment options that can improve functional outcome beyond the acute and subacute phase, although trials are ongoing regarding stem cell therapy and specific rehabilitation methods among other approaches [218, 225, 258]. Post-stroke fatigue has emerged in recent years as an issue that patients experience as debilitating and that can affect functional outcome [10]. Currently, a consensus is lacking on how to measure and quantify post-stroke fatigue, and knowledge is also scarce on the specific pathophysiology of fatigue after stroke and its treatment [191]. Future studies of post-stroke fatigue will be of value to improve outcome for stroke survivors long-term, as well as studies of cognitive and affective disorders that are associated with both fatigue and functional outcome [11]. To identify other problems that affect patients' lives after stroke and reduce stroke morbidity – it is important to continue measuring outcome with PROMs, to make sure that we identify treatment targets that are clinically meaningful for patients.

Populärvetenskaplig sammanfattning (Summary in Swedish)

Stroke är en folksjukdom som i Sverige drabbar cirka 25 000 individer per år och utgör den tredje vanligaste dödsorsaken. Dessutom är stroke den vanligaste kroppsliga orsaken till behov av långtidsvård. I begreppet stroke ingår plötsliga rubbningar av hjärnans funktioner som beror på antingen förhindrad blodtillförsel (vanligen p.g.a. blodpropp) till ett område i hjärnan (hjärninfarkt), eller att ett blodkärl brister och blödning skadar ett område i hjärnan (hjärnblödning).

Antalet nyinsjuknanden i stroke per år (även kallat incidens) har minskat i delar av västvärlden, men siffrorna varierar stort även inom Europa. De sista decennierna har betydande framsteg gjorts vad gäller akut behandling av stroke, liksom behandlingar för att förebygga stroke. Därför är det viktigt att uppdatera vår kunskap om vilka och hur många som insjuknar i stroke, och hur det sedan går för personerna som insjuknat.

Stroke kan i det akuta skedet ge problem med till exempel rörelseförmågan i armar, ben och/eller ansiktet, känselstörningar eller problem med synen eller talet – och dessa problem kan vara bestående. På lång sikt finns även andra möjliga följder såsom hjärntrötthet, depression, minnes- och koncentrationssvårigheter och svårigheter att självständigt klara sig i vardagen. Därutöver vet vi att risken är högre bland de som har haft en stroke att insjukna i en ny stroke, jämfört med normalbehandlingen.

I detta avhandlingsarbete, bestående av fyra delarbeten, studeras förekomsten av nyinsjuknanden i stroke, upptäckningsgraden av nyinsjuknanden i stroke hos två lokala sjukhusbaserade strokeregister, samt överlevnad, återinsjuknanden och utfall efter stroke i området kring Skånes Universitetssjukhus i Lund.

Vid Skånes universitetssjukhus i Lund finns två pågående sjukhusbaserade studier som kontinuerligt samlar information om de individer som diagnosticeras eller vårdas på sjukhuset på grund av stroke: Lund Stroke Register (LSR) och Riksstroke. I delarbete I gjordes en granskning av data från LSR och Riksstroke, men också databaser för primärvården, öppenvårdskliniker och bland obduktionsrapporter hos Avdelningen för Patologi och Rättsmedicinska avdelningen i Lund. Detta gjordes för att försöka identifiera samtliga fall av nyinsjuknande i stroke i studieområdet

under ett år mellan 2015–2016. Studieområdet utgörs av 8 kommuner omkring sjukhuset i Lund (Eslöv, Höör, Hörby, Lund, Staffanstorp, Burlöv, Kävlinge, och Lomma). Denna typ av metod kallas för populationsbaserad metodologi – och är värdefull för att säkerställa att man studerar hela befolkningen som insjuknar i stroke, och inte riskerar att dra felaktiga slutsatser för att man systematiskt har missat att studera en viss subgrupp av strokepatienter, till exempel de som aldrig kommer till sjukhus på grund av sin stroke. I delarbete I redovisas att 413 individer insjuknade i förstagångsstroke mellan mars 2015 och februari 2016. Om man justerar detta efter den totala studerade befolkningsstorleken och ålders- och könssammansättning (även kallat ålders- och könsstandardiserad incidens) innebär detta att 165 per 100 000 individer i studieområdet insjuknade i stroke under studieåret. Vid jämförelser med en tidigare studie i området från 2001-2002 kunde vi konstatera att detta innebär en 33-procentig minskning av incidensen av stroke i vårt område mellan 2001-2002 och 2015-2016. Dessutom minskade det totala antalet fall av stroke från 456 till 413. Dock minskade inte incidensen av hjärnblödningar, och inte heller incidensen av stroke bland de som var yngre än 65 år. Sammanfattningsvis tyder dessa resultat på att strokeincidensen minskar i vårt studieområde, liksom i flertalet andra höginkomstländer. Detta tros åtminstone delvis bero på bättre kontroll av strokeriskfaktorer som högt blodtryck och förmaksflimmer. Det kan emellertid behövas ett ökat fokus på förebyggande behandling av stroke hos unga samt hjärnblödningar – eftersom incidensen förblivit oförändrad i dessa subgrupper det senaste decenniet.

I delarbete II jämfördes de sjukhusbaserade studierna LSR och Riksstroke med den populationsbaserade studiegruppen som samlades in för delarbete I. Avsikten med delarbete II var att identifiera hur många och vilka patienter som missas med sjukhusbaserad insamling jämfört med populationsbaserad metodologi. Detta är viktigt, då sjukhusbaserade studier har i allt större utsträckning börjat användas för att uppskatta trender i förekomsten och epidemiologin av stroke. För att man säkert ska kunna göra detta är det värdefullt att också känna till vilka subgrupper av strokepatienter som man *inte* upptäcker och därmed inte studerar med sjukhusbaserade metoder. Riksstroke är ett nationellt strokeregister som omfattar alla sjukhus i Sverige som vårdar akuta strokepatienter, medan LSR är en lokal strokestudie som bland mycket annat studerar genetiska riskfaktorer för stroke. Därför skiljer sig metoderna även något mellan de två registren, där LSR har en mer komplett regelbunden screening av både neurologiavdelningar och -mottagningar, men även akutmottagningsbesök för att identifiera möjliga strokefall. Riksstroke använder i stället regelbunden screening av patienter som vårdas på neurologiavdelning, och övriga patienter upptäcks vid journalgenomgångar i efterhand. I delarbete II undersöktes bara de med hjärninfarkt och en viss typ av hjärnblödning (intracerebral blödning), varför det totala patientantalet i den populationsbaserade studiegruppen var 400. Resultaten i delarbete II visar att cirka

10–20% av strokepatienter riskerar att missas vid enbart sjukhusbaserad insamling. Framför allt riskerar man att inte upptäcka patienter som bor på särskilda boenden, som avlider tidigt utan att komma till sjukhus eller personer med lindriga stroke. Olika grupper av patienter tenderade dock att missas av LSR och Riksstroke, vilket tyder på att storleken och sammansättningen av patienter som inte upptäcks i ett register beror på den enskilda studiens metoder. Detta har stort värde för att kunna bedöma hur generaliserbara studieresultat från LSR och Riksstroke är, det vill säga hur väl dessa studier representerar befolkningen i stort.

I delarbete III följdes de 400 deltagarna med förstagångsstroke (hjärninfarkt eller intracerebral blödning) 2015–2016 upp avseende överlevnad, dödsorsaker och återinsjuknande. Totalt överlevde 265 personer (66%) 3 år efter det första insjuknandet, och överlevnaden var sämre bland de med hjärnblödning (55%) jämfört med hjärninfarkt (69%), och majoriteten av de som dog avled till följd av hjärt-kärlsjukdom (inklusive stroke, 57%). Jämfört med tidigare studier i vårt studieområde från 1980-, 1990- och 2000-talen har 3-årsöverlevnaden successivt förbättrats 10 procentenheter från 56% på 80-talet. Dock tycks takten som överlevnaden förbättras ha förlångsammats sista decenniet. I delarbete III redovisas även att totalt 8% i vår studiegrupp fick en ny stroke inom 3 år efter förstagångsinsjuknandet. Vid återinsjuknande i stroke var det vanligt (55% av fallen) att den bakomliggande orsaken till hjärninfarkt var en annan än vid förstagångsinsjuknandet, men i många fall kunde man inte fastställa en klar orsak till förstagångsinsjuknandet. Detta belyser vikten av noggrann utredning av bakomliggande orsaker till stroke för att kunna ge behandling som minskar risken för ny stroke. Dessutom behövs fortsatt uppföljning av långtidsöverlevnaden i stroke för att kunna planera vård för personer efter stroke och för att utvärdera effekter av införseln av nya akuta behandlingar för stroke på befolkningsnivå.

Slutligen, i delarbete 4 undersöktes överlevande strokepatienter efter 3–4 år avseende deras funktionsnivå och livskvalitet efter stroke. Av 249 som överlevde 3–4 år kunde 202 följas upp med antingen ett besök på sjukhuset eller i hemmet (180), eller via telefon (22). Resterande 47 personer kunde antingen inte nås eller avböjde uppföljning. Totalt hade 73% en god funktionsnivå, det vill säga att även om de hade kvarvarande symtom eller svårigheter att genomföra vissa av sina tidigare aktiviteter efter stroke – så kunde de sköta sina egna angelägenheter utan hjälp. Därtill rapporterade 69% att de skattade sitt eget hälsotillstånd som gott eller mycket gott. Trötthet (fatigue) efter stroke var associerat till både att ha svårare att sköta sina vardagliga uppgifter, och sämre självupplevd hälsa. Trots att många strokeöverlevare hade god funktionsnivå och skattade sin egen hälsa väl rapporterade fler än 3 av 10 att de hade svårt att genomföra vissa vardagliga aktiviteter. Resultaten i delarbete 4 visar att även om förekomsten av stroke och överlevnaden efter stroke har förbättrats sista decennierna, så finns det mycket man kan förbättra avseende livet efter stroke. För närvarande saknas det effektiva

behandlingsmetoder som kan förbättra funktionsnivån i det kroniska stadiet av stroke, och det saknas även effektiv behandling för trötthet efter stroke – som är ett ofta dolt symptom som medför funktionsförsämring och nedsatt självupplevd hälsa. Ökade insatser för att för att förbättra livet för de som överlever en stroke är viktigt då flera tidigare studier har prognosticerat en ökad total börda av stroke i världen över de kommande decennierna i takt med en åldrande befolkning.

Sammantaget visar den här avhandlingen att samtidigt som framsteg görs vad gäller att förebygga stroke och förbättra utfallet av akut stroke, så finns det subgrupper som hjärnblödningar där samma förbättringar inte ännu har skett. Dessutom finns mycket kvar att förbättra för de som överlever sin stroke och lever med följdtillstånd som trötthet och nedsatt funktionsnivå.

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About the author

Joseph Aked is an internal medicine resident at Blekinge Hospital in Karlskrona, Sweden. This doctoral dissertation explores trends in stroke epidemiology in southern Sweden, as well as the clinical long-term outcome for the affected individuals, in order to better understand how stroke morbidity can be alleviated in the future.

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