REGISTRY-BASED STUDIES OF RETURN TO WORK AFTER STROKE

– PART OF THE WORK AFTER STROKE STUDY (WASS)

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Gothenburg, Sweden, 2021

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Cover illustration by Anna Karlsson

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ISBN 978-91-7833-988-4 (PRINT)
ISBN 978-91-7833-989-1 (PDF)
http://hdl.handle.net/2077/66816

Printed in Borås, Sweden 2021
Stema Specialtryck AB

We should be taught not to wait for inspiration to start a thing. Action always generates inspiration. Inspiration seldom generates action.
– Frank Tibolt

ABSTRACT

Objectives. Stroke is one of the most common diseases and a main cause of disability both globally and in Sweden. Even though the risk increases with older age, stroke in the younger population is increasing and a substantial part of those who suffer from stroke are at working age. Stroke in this group entails several consequences for the affected person as well as for the society as a whole. To be able to participate in work life is important from the economic perspective and seem to affect several aspects of health. National guidelines of sickness absence after stroke in Sweden suggests potential sick leave up to 2 months on full-time after stroke, however there is a lack of research investigating this topic. The aim of the thesis was to investigate in what time period people return to work (RTW) after stroke, what factors are associated with higher and faster RTW, and if RTW status affects the individual in several aspects of health post-stroke.

Methods. The four individual papers mainly had long-term perspectives with follow-up times ranging between 18 months and 6 years post-stroke. They all include data pooled from different Swedish registries, and all participants had a first-time stroke during working age. Paper I and II are based on local cohorts from the Sahlgrenska University hospital in Gothenburg, Sweden, and paper III and IV on the Swedish national quality registry called Riksstroke. Working capacity prior to stroke and RTW after stroke was assessed based on sickness absence data from the Social Insurance Agency. Furthermore, questionnaire surveys, medical records, registries from the National Board of Health and Welfare, and registries from Statistics Sweden were the other data sources that were used. The statistical methods include logistic regression, Kaplan-Meier curves, Cox regression and shift analysis. All papers have ethical approval from the Regional Ethical Review Board in Gothenburg.

Key results. The majority of all the participants did RTW, and most did so within the first two years after stroke. For some participants, however, the RTW process continued for several years post-stroke. A number of different factors, including demographical, stroke related, and socioeconomic factors, were important for RTW. For example, milder stroke severity, ischemic stroke compared to intracerebral haemorrhage, male sex, younger age, and higher educational level were significant determinants for RTW. In addition, those who had self-expectations of RTW were more likely to RTW compared to those who did not have expectations of RTW and the participants who were on sick leave for more than 2 weeks the year before the stroke had lower odds of RTW compared to the participants that were not on sick leave prior to stroke. The participants that did RTW had a better self-perceived health-related quality of life and general health, as well as less symptoms of depression and pain compared to the participants who did not RTW. However, the RTW-group at 1 year post-stroke had a decline in general health and increased pain between the 1 and 5 year follow-up post-stroke, which was not found in the no-RTW group.

Conclusions. The process of RTW could continue for a longer time after stroke than previously described. Several different factors, both modifiable and non-modifiable, are important for RTW. RTW is perhaps not solely a facilitator of health, but should be seen as a more complex process. The present results could hopefully guide health care professionals and government authorities to further optimise and individualise the RTW process for the affected persons.

Keywords

Stroke, Return to work, Working age, Rehabilitation, Cerebrovascular Diseases, Ischemic stroke, Intracerebral haemorrhage, Registries

POPULÄRVETENSKAPLIG SAMMANFATTNING

Stroke är en av de vanligaste folksjukdomarna och kan ha stora konsekvenser i form av till exempel fysiska nedsättningar, kognitiva svårigheter och psykologiska problem hos den drabbade individen. En betydande andel av personerna som drabbas av en stroke i Sverige är i arbetsför ålder och för dessa personer är det viktigt att belysa arbetsåtergång. Arbete är inte bara en inkomstkälla utan även betydande för en persons identitet och hälsa i stort. Även för samhället är arbetsåtergång efter stroke av stor betydelse då kostnader för sjukskrivning och produktionsbortfall står för en väsentlig andel av de totala kostnaderna för stroke i Sverige. Denna avhandling syftade till att undersöka under vilken tidsperiod arbetsåtergång efter stroke sker, vilka faktorer som påverkar vem som återgår och hur snabbt det sker, samt hur personers mående i efterförloppet av stroke påverkas beroende på om hen återgått till arbete eller inte.

För att undersöka arbetsåtergång har flera olika register kombinerats, och enkäter analyserats. Samtliga studiedeltagare hade haft en förstagångsstroke i arbetsför ålder, och i delstudie 1 och 2 har deltagarna vårdats på Sahlgrenska Universitetssjukhuset medan det i studie 3 och 4 används heltäckande nationella studiepopulationer. Arbetsförmåga innan stroken och arbetsåtergång efter stroken definieras i samtliga ingående studier utifrån sjukskrivningsdata från försäkringskassans register. Även data från register hos socialstyrelsen och statistiska centralbyrån har använts, och data har också inhämtats från patientjournaler. Studierna i denna avhandling har främst haft ett långtidsperspektiv med uppföljningstider mellan 18 månader och 6 år efter insjuknande i stroke.

Resultatet från studierna visar att majoriteten av studiedeltagarna som är i arbetsför ålder, återgår till arbete efter stroke och de flesta återgår inom relativt kort tid (1-2 år) efter insjuknande. För

en liten grupp dröjer dock arbetsåtergången flera år efter stroke, upp till 3-4 år för vissa. Flera olika faktorer så som kön, ålder, utbildningsnivå, sjukskrivning före stroke, stroketyp, strokens svårighetsgrad och förväntningar kring återgång inverkar i vilka som återgår i arbete och hur snabbt det sker. De som återgått i arbete mådde bättre i flera hälsoaspekter både vid 1 och 5 år efter stroke jämfört med de som inte återgått i arbete. Detta gäller tex självskattad livskvalitet, generell hälsa, upplevd smärta och nedstämdhet. Däremot självskattade de som återgått i arbete inom 1 år en klar försämring i generell hälsa och smärta mellan 1 och 5 år, medan de som inte återgått inte upplevde någon försämring.

Arbetsåtergång efter stroke är en komplex men viktig fråga. Denna avhandling visar att det kan ta tid innan återgång i arbete är möjligt, och denna tid till arbetsåtergång är ett relativt nytt fynd som inte helt är i linje med dagens beslutsstöd för sjukskrivning som svenska myndigheter tillhandahåller. Flera olika faktorer är viktiga för arbetsåtergång, både modifierbara faktorer och sådana faktorer som inte går att påverka. Även om de som återgått i arbete mådde bättre i flera hälsoaspekter än de som inte återgått så verkar arbetsåtergång i sig inte enbart vara en positiv faktor för hälsa. Denna forskning kan förhoppningsvis vara till nytta för sjukvårdspersonal och svenska myndigheter och bidra till en mer individualiserad och riktad rehabilitering och sjukvård för att optimera arbetsåtergångsprocessen efter stroke.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals. All papers are open access, which permits the reproduction in the thesis.

I. **Westerlind E**, Persson HC, Sunnerhagen KS. Return to Work after a Stroke in Working Age Persons; A Six-Year Follow Up. *PLoS One*. 2017;12(1):e0169759

II. **Westerlind E**, Abzhandadze T, Rafsten L, Persson HC, Sunnerhagen KS. Very early cognitive screening and return to work after stroke. *Topics in Stroke Rehabilitation*. 2019;26(8):602-7

III. **Westerlind E**, Persson HC, Eriksson M, Norrving B, Sunnerhagen KS. Return to work after stroke: A Swedish nationwide registry-based study. *Acta Neurologica Scandinavica*. 2020;141(1):56-64

IV. **Westerlind E,** Persson HC, Palstam A, Eriksson M, Norrving B, Sunnerhagen KS. Differences in self-perceived general health, pain, and depression 1 to 5 years post-stroke related to work status at 1 year. *Scientific Reports*. 2020;10(1):13251

LIST OF RELATED PAPERS

Papers related to the subject but not included in the thesis, that I have authored/co-authored during my PhD studies. Referred to in text by their lowercase Roman numerals.

i. Palstam A, **Westerlind E**, Persson HC, Sunnerhagen KS. Work-related predictors for return to work after stroke. *Acta Neurologica Scandinavica*. 2019;139(4):382-388

ii. **Westerlind E**, Persson HC, Tornbom K, Sunnerhagen KS. Return to work predicts perceived participation and autonomy by individuals with stroke. *Disability and Rehabilitation*. 2019:1-6

iii. **Westerlind E**, Persson HC, Sunnerhagen KS. Working capacity after a subarachnoid haemorrhage: A six-year follow-up. *Journal of Rehabilitation Medicine*. 2017;49(9):738-743

iv. Willers C, **Westerlind E**, Borgström F, von Euler M, Sunnerhagen KS. Health insurance utilization after ischemic stroke in Sweden: a retrospective cohort study in a system of universal healthcare and social insurance. *Submitted*

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ABBREVIATIONS

RTW	Return to work
GOTVED	Gothenburg Very Early Supported Discharge Study
SALGOT	Stroke Arm Longitudinal Study at the University of Gothenburg
IS	Ischemic stroke
ICH	Intracerebral haemorrhage
ICF	International Classification of Functioning, Disability, and Health
ICD-10	International Classification of Diseases, 10th revision
MoCA	Montreal Cognitive Assessment
NIHSS	National Institutes of Health Stroke Scale
RLS	Reaction Level Scale
mRS	modified Rankin Scale
OR	Odds ratio
HR	Hazard ratio
95 % CI	95 % confidence interval
SD	Standard deviation

INTRODUCTION

Stroke is a disease with substantial consequences for the affected person and a large burden on society (1). The proportion of people having a stroke in working age is increasing (2, 3), and sickness absence due to stroke is an important aspect to consider both for the individual (4) and for the society (5). Swedish national guidelines today suggest sick leave up to 2 months on full-time after stroke (6), but support for this in current research is vague as there is not sufficient data. More research is needed to describe the complex picture of return to work (RTW) after a stroke in working age, and Sweden has a unique opportunity to use registry data in the quest for this aim.

Stroke

Definition and sub types

Stroke has traditionally been defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" according to the World Health Organization (7). Efforts has been made to develop and update the definition of stroke for the 21st century, specified for each sub type. The two main types of stroke are ischemic stroke (IS) and intracerebral haemorrhage (ICH). IS is defined as: "An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction", and ICH as: "a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma" (8). In addition to IS and ICH, subarachnoid haemorrhage is sometimes noted as a third stroke type but is not included within the scope of the present thesis.

IS counts for approximately 85 % of all stroke diagnoses in Sweden (9), but the percentage is somewhat lower globally (10). IS is mainly

caused by large-artery atherosclerosis (e.g. carotid stenosis), cardioembolism, or small-vessel occlusion (11). Risk factors include hypertension, diabetes mellitus, cardiac disease (e.g. arterial fibrillation), smoking and alcohol intake (9, 12).

ICH is the second most common sub-type of stroke. The risk factors for ICH are fairly similar to those for IS, including hypertension, diabetes mellitus and alcohol intake (13). Treatment with anticoagulants entails a risk of more severe ICH (14).

Incidence globally

There is a trend showing a shift of high global burden from infectious and nutritional diseases, to non-communicable diseases such as stroke (15). Stroke is one of the most common diseases in the world with a substantial burden on society. In 2013, it was the second largest cause of death and the third most common cause of disability globally (1). Worldwide, the age-adjusted annual incidence was 258 cases per 100 000 person-years in 2010 (16). The number of persons affected by stroke is increasing globally and this is likely due to an aging population and an increase in modifiable risk factors such as high blood pressure, high BMI, and low physical activity (1). Furthermore, due to improvement in stroke care, the survival rate is increasing (1), which means a growing number of people living with the consequences of stroke. The incidence of stroke is increasing in young and middle-age patients, while it is decreasing in the older population (2). Due to this, the global burden of disease group suggest that stroke should not only be considered as a disease of the elderly anymore (1).

Incidence in Sweden

In Sweden, approximately 25 000 people have a stroke each year (17). In 2018, the majority (54 %) were men and the mean age at the time of stroke were approximately 75 years (9). There is a decrease in stroke incidence in persons aged ≥ 65 years over the last decades, however there is an increase or unaltered incidence in the working age population in Sweden (3, 18). Almost 1 out of 4 of the people

having a stroke in Sweden between 2005-2010 suffered from the stroke when younger than 65 years of age (18).

Consequences of stroke

Stroke is a disease that entails a risk of severe sequelae of varying kind. Physical impairments are perhaps the most well-known, but there is also a substantial risk of cognitive impairments (19) psychological problems (20, 21), and post-stroke pain (22). Post-stroke impairments commonly have consequences for the affected person's life, for instance on their participation in the society (23, 24). The recovery after stroke varies between people. A review article has suggested that the recovery trajectories of body functions and activities show a fast recovery the first weeks after stroke that gradually plateaus at 6 months, after which some people continue to improve, while others decline in function (25). Several studies support the hypothesised deterioration in function with results showing a long-term decline in, for instance, activities of daily living (ADL), self-efficacy, optimism, and self-reported function, after the initial improvement (26-28).

Stroke care

The acute care after an IS has undergone a distinct change the last decades with reperfusion treatment (thrombolysis and thrombectomy) becoming more common (29). Reperfusion treatment aims at removing the thrombus or embolus causing the ischemia in an IS, and thereby enabling a reperfusion to the affected area in the brain (30). This has been shown to have a significant positive effect in the outcome and recovery of IS (31-34). Another development in stroke care are stroke units, which were established in the latter part of the 20th century (35, 36). A stroke unit is an identifiable unit (usually a hospital ward) with a multidisciplinary team dedicated to stroke patients performing organised stroke care (37). The team involves a physician, nurse, assistant nurse, physiotherapist, occupational therapist, social worker, speech therapists, dietician, and psychologist (38). This enables an early start of rehabilitation after stroke in combination with the acute treatment. Hence, patients treated at a stroke unit have been shown

to have less mortality and less functional dependency than patients treated at other wards (37). Today, the vast majority of patients with stroke in Sweden are admitted to a comprehensive stroke unit (9). In 2018, the percentage of patients with stroke treated at a stroke unit were 92 % in Sweden, and these patients were younger than the eight percent of patients with stroke treated at other hospital wards (9).

The rehabilitation after stroke is ideally multifaceted and includes medical treatment together with occupational therapy, physical therapy, speech and language therapy, and psychological treatment (39) to address not only neurological impairments but also activity limitations and restriction in participation. For working age people, areas like family-life and employment are of importance and need attention (40). Participation in society, for instance RTW, could be seen as one of the main goals for rehabilitation post stroke (41). The amount and length of rehabilitation in general, and more specifically vocational rehabilitation, varies between countries and between patients (9, 39, 42).

Costs for society

Stroke is a resource intensive disease. The costs of stroke to society was estimated to be 18.3 billion Swedish crowns in Sweden in 2013 (43), a number that did not include the costs of next of kin to the affected person, which has been shown to be substantial (44). Stroke care has been estimated to constitute of approximately 4 % of the total healthcare expenditures in Sweden (5). Furthermore, about 21 % of the total costs for stroke were indirect costs in 2009 (5). Indirect costs mean production losses for death, early retirement, and sick leave. The indirect costs were higher for men (30 %) than women (14 %) (5). The results from related paper iv also include similar sex differences. Related paper iv furthermore showed that the average indirect costs per person the first year after stroke were between 11 600 and 18 000 Euro depending on age group, and the indirect costs were highest the first year after stroke compared to the second year.

International Classification of Functioning, Disability and Health

The International Classification of Functioning, Disability and Health (ICF) was published by the World Health Organization in 2001 (45, 46). The ICF is a framework for describing changes in body function, capacity and performance due to a health condition, in a bodily, individual, and societal perspective (45). The biopsychosocial model of disability in ICF (figure 1) includes a disease (health condition), functioning and disability (body functions, activities, and participation), and contextual factors (environmental factors and personal factors) (45). After a stroke, several body functions, activities, and participation areas including gainful employment, in accordance with the ICF, can be affected (25). The framework can be used both in clinical setting and in research to handle data in a standardised way. All of the components in the model are considered in the present papers and in the thesis.

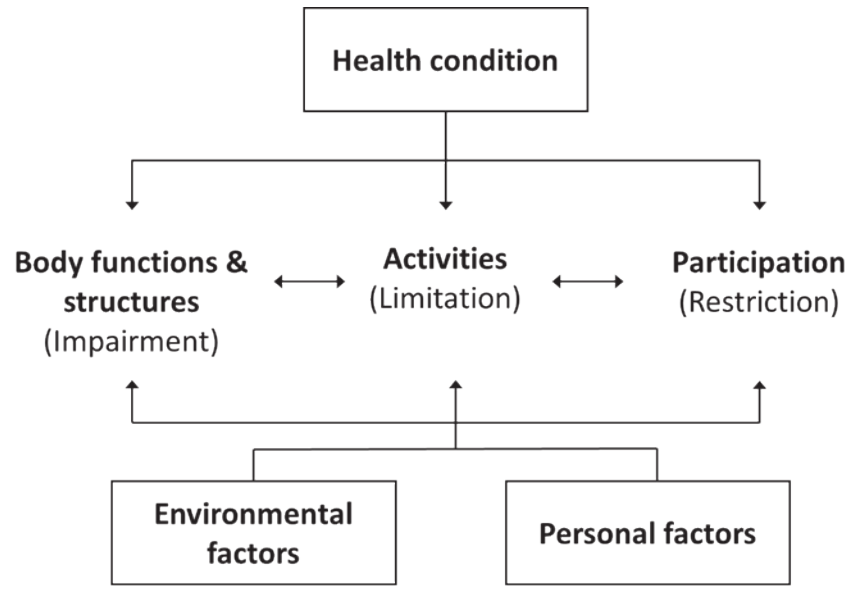

Figure 1. The International Classification of Functioning, Disability and Health (ICF) model.

Work

The concept of work can contain various activities such as employment, self-employment, voluntary work, and household work. In Sweden, work is generally referred to as gainful employment, which is in line with the approach in the present thesis.

Work ability and work disability are concepts without a clear definition and previous research present no consensus about its nature (47). Work ability has been described as an interaction between human resources and work factors (48). The human resources include health and functional capacity, education and competence, values and attitudes, and motivation (48, 49). Work factors are for instance work environment, demands, and management (49). All these dimensions influence each other.

Work is an important part of life for the majority of working age people. Besides the financial aspect, work seem to be important for creating an identity (50). It is perhaps particularly important in countries like Sweden, where the work role is an essential aspect in forming the role in social contexts. Work have been shown to correlate with many of the dimensions of health-related quality of life (51-54), and not working could also be a risk factor of having a stroke (55). Conversely, work-related factors could have an adverse effect on an individual's health as well. For instance, work-life stress has been shown to relate to health risk behaviours such as smoking, physical inactivity and less sleep (56). Furthermore, to work while being sick, referred to as sickness presenteeism, has been associated with both worse health, and sickness absence in the future even after adjusting for other factors such as previous sickness absence and working capacity (57, 58).

Sickness absence

Reduced health could lead to sickness absence from work. Different concepts are used to define ill health, e.g. illness, disease and sickness (59). Illness is used when a person experience reduces health, which could be related to actual severe health problem (60), but does not have to be. Disease is something that is diagnosed by a healthcare worker, e.g. a physician. Sickness is defined as the role in

society a person with illness or disease is given. This concept is closely related to sickness absence, which often is used to assess reduced health (61). Previous research suggests that the overlap between the concepts illness, disease and sickness are quite low (59).

In Sweden, sickness absence is linked to the disease concept. A diagnosis based on the International Classification of Diseases (ICD-10) (62) system is required in order to receive sickness benefit or sickness compensation from the Social Insurance Agency (Försäkringskassan). The diagnosis must also result in problems that hinders the person to be productive at work. The Social Insurance Agency is a public authority in Sweden that provides financial compensation during sickness absence to people with all kinds of occupations, parental leave or unemployment. The first 2 weeks of absence, the employer provides sickness pay, after that the Social Insurance Agency steps in. The financial compensation from the agency consists of either sickness benefit (sick leave) or sickness compensation (early retirement). Sickness compensation is provided when a person is unlikely to ever RTW, usually only applicable after a longer period of sickness benefit. Both sickness benefit and sickness compensation are distributed at 25 %, 50 %, 75 % or 100 %. The Social Insurance Agency uses a step-by-step model with more stringent criteria the longer time of absence from work, when deciding who is granted financial compensation.

The National Board of Health and Welfare (Socialstyrelsen) provides guidelines (Försäkringsmedicinskt beslutsstöd) in collaboration with the Social Insurance Agency on length and amount of sickness absence for different diagnoses to guide physicians in writing medical certificate and social insurance agents in approving compensation. For stroke, the recommendations are to provide sick leave up to 2 months on full-time (6).

Return to work after stroke

As early as in 1965-1971, the RTW after a stroke in working age was investigated in Gothenburg, with a RTW rate of approximately 40 % after stroke (63). The possibility of RTW after a stroke in working age persons vary largely in more recent research, and numbers between 7 % and 88 % have been presented in several review articles

(64-66). These frequencies are from different countries with different methods (64). For instance, the follow-up times differ, with 1-2 years being the most common timeframe (64). Furthermore, RTW is assessed and defined in different ways (e.g. self-reported or registry-based), resulting in variable outcomes.

Predictors of return to work

Stroke severity, including both physical and cognitive impairments, has perhaps been the most consistent predictor of RTW in previous research (67-71). Cognitive function, mainly assessed after the acute phase of stroke has also been a significant determinant of RTW (72-75). Stroke type has been an important factor in some studies, where people with ischemic stroke were more likely to RTW than people with haemorrhagic stroke (76, 77). On the other hand, some studies show no significant difference between stroke types (70, 78).

Demographical factors such as age and sex are often significant in prediction of RTW. Male sex (70, 79-81) and younger age (80, 82) have been favourable, even if there are inconsistent findings particularly with age as a determinant (67, 78, 83).

Socioeconomic factors have shown varying results in previous studies. Higher income has been a positive predictor for RTW (81) and educational level has been both significant (76, 81) and non-significant (70, 78). Furthermore, related paper iv indicates that there are socioeconomic differences in utilization of health insurance in Sweden as people in the lowest income quartile received less health insurance than people with higher income did after stroke.

One of the most consistently reported work-related predictors for RTW is qualification level, where being a white-collar worker seems favourable (69, 76, 84, 85). Related paper i, which is based on the same data as paper I, showed that having a qualified occupation was important for RTW in men, but not in women, after a stroke (86). Furthermore, being self-employed (76), or working at a larger enterprise (87) have been positive predictors of RTW.

Impact of RTW on the individual

To be able to RTW after a stroke in working age is important for life satisfaction and subjective well-being (4, 85). Other factors associated with RTW are higher quality of life, and less depression (88, 89). Related paper ii presented an association between RTW and higher participation and autonomy in society as a whole (90). Studies have however also shown that people suffering from a stroke experience mixed feelings when returning to work. Frustration and insecurity are mixed with satisfaction and happiness (91, 92).

Registry-based studies

Sweden, as well as the rest of the Nordic countries, have a unique opportunity for registry-based studies due to several reasons (93-95). The healthcare is tax funded and available to all citizens, and there are numerous comprehensive databases operated by authorities and quality registries. In addition to this, all Swedish citizens have a unique personal identification number that enables data to be pooled from different data sources. The Swedish government emphasises the need for increased registry-based research and has decided to facilitate the use of registry data in research (93, 96).

An advantage with registry data is that it usually comprises the vast majority of the people intended to study. Therefore, the risk of selection bias is lowered. Furthermore, registries can give exact data on, for instance, the number of days until an event.

Swedish registry data were used to investigate RTW after a stroke decades ago (63), where data from the stroke register in Gothenburg and data from the Social Insurance Agency were used. More recent research in this field however mainly use other kinds of data, such as self-reported, instead of registry data to answer the research questions.

Knowledge gap

The recommendation from the National Board of Health and Welfare in collaboration with the Social Insurance Agency is full time sick leave up to 2 months following a stroke (6). There is, however, a lack of studies investigating time to RTW, and most research about RTW after stroke have short follow-up times of 1-2 years (64). Furthermore, what factors influence RTW is not completely established and previous research sometimes show contradictory results (66, 97). To be able to RTW have mostly been proven to have a positive effect on the individual (4, 85, 88), but there has also been indications in qualitative studies that it is not always solely positive (91, 92). There is a lack of quantitative studies investigating the effect of RTW status on different aspects of the individuals' health over time.

AIMS

The overall aim of this thesis was to investigate RTW in persons having a stroke at working age. The specific aims of the individual papers included in the thesis were:

I. Investigate in what time period stroke survivors continue to RTW, in a long-term perspective. Furthermore, analyse factors associated with RTW, as well as potential differences in self-reported quality of life between those who have returned and those who have not.

II. Investigate amount of RTW after stroke, and whether screening of cognitive function (both global cognitive function and executive function) very early after stroke can predict RTW at different time-points.

III. Investigate in what time period stroke survivors continue to RTW, possible predictors of RTW including demographical, stroke-related, and socioeconomic factors, as well as self-reported expectations of RTW, in a comprehensive national population with a long-term perspective.

IV. Investigate if there is any difference in self-perceived general health, pain, and depression between 1 year and 5 years post-stroke in people who have RTW compared to people not RTW after a stroke.

METHODS

Study design

The four individual papers included in the thesis are observational registry-based cohort studies with a retrospective design. They all mainly have long-term perspectives, and as seen in table 1, with follow up times ranging between 18 months and 6 years post-stroke.

Table 1. Inclusion period and follow-up time of the individual papers.

	Paper I	Paper II	Paper III	Paper IV
Inclusion period	2009-2010	2011-2016	2011	2011
Overall follow-up time	6 years	18 months	5 years	5 years
Questionnaire follow-up time	5 years	-	1 year	1 and 5 years

Study population and data sources

All papers involve registry data that were linked based on the participants personal identification number. The pooling of the registries is presented in figure 2.

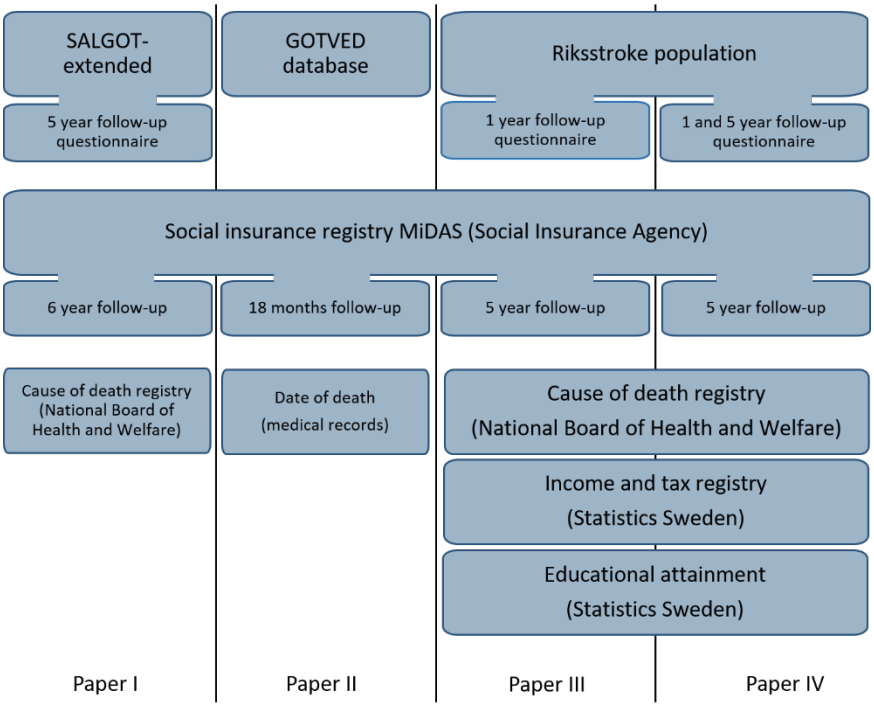

Figure 2. The data sources and registries used in the present papers. Abbreviations: SALGOT: Stroke Arm Longitudinal study at the University of Gothenburg; GOTVED: Gothenburg Very Early Supported Discharge; MiDAS: MikroData för Analys av Socialförsäkringen.

Paper I and paper II are based on local cohorts at Sahlgrenska University Hospital in Gothenburg, Sweden, while paper III and paper IV are based on the Swedish Stroke Register (Riksstroke) (table 2). In paper I, the participants were extracted from the Stroke Arm Longitudinal study at the University of Gothenburg (SALGOT)-extended study (98-100). The participants in paper II were extracted from the Gothenburg Very Early Supported Discharge (GOTVED) study (101) database, and Riksstroke was the origin of the study populations in paper III and IV. All study populations included people with a first ever stroke (i.e. ischemic stroke and intracerebral haemorrhage, not subarachnoid haemorrhage) at working age. In paper IV, the participants that were deemed not to have working capacity prior to the stroke (sickness compensation > 50 %) were excluded from the study. The other three

papers included the participants with sickness compensation prior to stroke to enable the presentation of sickness absence pattern in the stroke population. However, the participants not deemed to have sufficient working capacity prior to stroke were excluded before RTW analyses in all papers.

Table 2. Study population of the included papers.

	Paper I	Paper II	Paper III	Paper IV
Size of study population	211 people	145 people	1968 people	398 people
Data source	SALGOT	GOTVED	Riksstroke	Riksstroke
Inclusion criteria	•First ever stroke (ICD-10 I61 or I63) •Age 18-63 •Treated at a stroke unit, neurosurgical unit or intensive care unit at Sahlgrenska University Hospital, Sahlgrenska •Live within 35 km from hospital	•First ever stroke •Age 18-63 •Treated at a stroke unit at Sahlgrenska University hospital, Sahlgrenska •Complete data on the MoCA 36-48 h after admission	•First ever stroke (ICD-10 I61, I63 or I64) •Age 18-58	•First ever stroke (ICD-10 I61, I63 or I64) •Age 18-58 •Participated in 1 year and 5 year follow-up questionnaire survey
Exclusion criteria	•ICD I60	•ICD I60	•ICD I60 •Living in a nursing home when the stroke occurred	•ICD I60 •Living in a nursing home when the stroke occurred •> 50% sickness compensation the year before the stroke

Abbreviations: SALGOT: Stroke Arm Longitudinal study at the University of Gothenburg; GOTVED: Gothenburg Very Early Supported Discharge; ICD International Classification of Diseases; MoCA: Montreal Cognitive Assessment.

The SALGOT-extended and GOTVED are both research databases from Gothenburg. The SALGOT-extended consists of demographical (e.g. sex and age) and stroke-related data extracted from medical records, and a 5-year follow-up postal questionnaire survey investigating life after stroke, for example quality of life, participation and autonomy, and recovery after stroke. A registered stroke diagnosis in the medical records was the reason for inclusion in SALGOT-extended. The GOTVED database involves demographical and stroke-related data from medical records and clinical examinations. In GOTVED, healthcare professionals at Sahlgrenska hospital did the screening and inclusion of participants and performed assessments in eligible cases.

Riksstroke is a national quality registry for stroke in Sweden. All hospitals admitting acute stroke patients are connected and provide data to the registry. Riksstroke has a high coverage rate of > 90 % of all persons having a stroke and being treated at a hospital in Sweden (102). The registry includes patients with IS and ICH, and from 2020, also patients with subarachnoid haemorrhage. Since 2013, Riksstroke's annual report also involves patients with transient ischemic attack (43). The registry contains background data, stroke-related data and follow-up data. Background and stroke-related data from the acute phase are entered into the registry by healthcare professionals (103). A 3 months follow-up questionnaire survey by Riksstroke is filled out either by the affected person or with help from healthcare professionals (104). A 1 year follow-up questionnaire survey is sent out by postal mail to all surviving persons registered in Riksstroke every year, and an additional 5 year follow-up questionnaire survey was sent out to all people registered in Riksstroke with stroke during 2011.

The Social Insurance Agency is a public authority in Sweden that provides financial compensation during sickness absence to individuals with all kind of occupations, parental leave or unemployment. The registries contain data on exact number of days and extent of sickness benefit and sickness compensation that an individual has been granted.

To handle death during the study period, the Cause of Death Registry from the National Board of Health and Welfare in Sweden were used. Data on date of death were collected from the cause of death

registry in paper I, III and IV. In paper II, medical records were used for information about death during the study period.

In paper III and IV, information about socioeconomic factors such as income and educational level were collected from registries from Statistics Sweden. Statistics Sweden collects data on people with a Swedish personal identification number.

Variables

Predictors

Stroke severity

The National Institutes of Health Stroke Scale (NIHSS) is commonly used to assess stroke severity both in the hospitals and in research (105, 106). It is an ordinal scale that generates a score of 0-42 where lower score means less neurological impairment. The scale has had consistently good ability to predict the outcome after stroke (107, 108). The neurological functions tested include level of consciousness, eye movement, visual field, motor function, sensory function, language, speech, and inattention. The NIHSS was used to assess stroke severity in papers I and II. In paper II, the variable was dichotomised into very mild stroke (NIHSS 0-2) and higher NIHSS (NIHSS > 2). In Riksstroke, there is a large proportion of missing NIHSS data, which was why the Reaction Level Scale (RLS) (109) instead was used as a proxy for stroke severity in paper III and IV. The RLS measures consciousness in 8 levels. Level of consciousness has successfully been used as a proxy for stroke severity in previous studies, as it has been proven to compare well to the NIHSS as a predictor for mortality (110). The variable was divided into alert (RLS 1), drowsy (RLS 2-3), and unconscious (RLS 4-8).

In paper I, the modified Rankin Scale (mRS) was used to assess functional dependency at discharge from hospital. The mRS gives a score of 0-6, where lower score is better (111). It has been proven to be valid and reliable in previous research (112). The scale was

dichotomised into functionally independent (0-2) and functionally dependent (3-6) (113).

Socioeconomical factors

Different socioeconomic factors were investigated as potential predictors of RTW in paper III. These factors were country of birth, educational level and income. Country of birth were divided into Sweden, Nordic countries (except for Sweden), European countries (except for the Nordic countries) and countries outside of Europe. Educational level was divided into primary school (≤ 9 years), secondary school (10-12 years), short university education (13 years) and long university education (≥ 14 years). Income was analysed as the individual's portion of disposable household income divided into tertiles: low, medium and high income.

Very early cognitive function after stroke

Cognitive function was screened for within 36-48 hours of hospital admission by an occupational therapist using the Montreal Cognitive Assessment (MoCA) (114) in paper II. The MoCA is a screening tool with good validity and reliability that generates a score of 0-30 where higher score indicates better cognitive function, and a score of < 26 indicates impaired cognitive function (114). The MoCA comprises six cognitive domains: short-term memory, visuospatial abilities, executive functions, attention/concentration/working memory, language, and orientation. Total global cognitive function and an extraction of the executive function domain were analysed separately in the study.

Self-expectations of return to work

Self-expectations of RTW were investigated in paper III among the participants that still had not RTW within the first year after stroke. The question *Have you returned to work* from the 1 year follow-up questionnaire survey by Riksstroke were used, with the possible answers as: *No* / *No but I am planning to return to work* / *Yes but in less extent than before the stroke* / *I do not know*. The aim was solely to compare the participants that still had not RTW but expecting to RTW with the participants that still had not RTW but were not

expecting to RTW. Therefore, only the people answering either *No* or *No but I am planning to return to work* were included in the analysis and two groups not expecting to RTW and expecting to RTW, respectively, were created.

Outcome variables

Return to work

Sickness absence data from the Social Insurance Agency's registries were used to define RTW in all the papers. With small variations between papers, RTW was defined as ending a registration with sickness benefit or sickness compensation without entering a new registration, dying, or old-age retiring (turning 65 years old) for a predefined period of time. In paper I, only full RTW (meaning not receiving sickness benefit or sickness compensation to any extent) was counted as RTW. In paper II, both full RTW (as in paper I) and partial RTW (maximum 50 % sickness benefit/sickness compensation) was analysed. In paper III and IV, RTW was defined as not receiving more than 50 % of sickness benefit or sickness compensation.

Quality of life

Health-related quality of life was assessed in paper I using the EuroQol-5dimensions (EQ-5D) as part of the 5 year follow-up questionnaire survey in SALGOT-extended. The EQ-5D includes the domains mobility, self-care, usual activities, pain/discomfort and anxiety/depression (115). The scores in all the domains were recalculated into a single value representing health-related quality of life for each of the participants. A Swedish tariff were used for the calculation (116). Furthermore, the EQ-5D includes a visual analogue scale generating a score of self-rated health of 0-100.

Self-perceived depression, pain and general health

Self-perceived depression, pain and general health in paper IV were assessed using the 1 year and 5 year follow-up questionnaire surveys from Riksstroke. Depression was investigated by the question *Do*

you feel depressed with the answers *Never or almost never* / *Sometimes* / *Often* / *Constantly*. Pain was assessed by *Do you have any pa*in with the answers *Never or almost never* / *Sometimes* / *Often* / *Constantly*. The question *How would you assess your general health* with answers *Very good* / *Quite good* / *Quite poor* / *Very poor* was used for general health.

Statistical methods

The data in all the papers were processed and analysed in IBM SPSS Statistics version 22 and 25 (IBM Corp., Armonk, NY, USA). For all the statistical analyses, the significance level (alfa) was set at 5 %. Two-tailed tests and mainly non-parametric statistical tests were used. The main statistical tests used in the individual papers in the thesis are presented in table 3.

Table 3. Statistical analyses used in the individual papers.

	Paper I	Paper II	Paper III	Paper IV
Group comparisons				
Mann Whitney U test	X	X	X	X
Fischer´s exact test	X		X	X
Chi-squared test		X		
Time to event analyses				
Kaplan-Meier curves	X		X	
Log rank test	X			
Prediction analyses				
Logistic regression (including Spearman's correlation test, Hosmer Lemeshow test, ROC curves)	X	X	X	X
Cox proportional hazards regression (including proportional hazard assumption check and time-dependence check)	X		X	
Change over time analyses				
Shift analysis (including Wilcoxon signed rank test)				X

Abbreviations: ROC: Received Operating Characteristics.

To analyse differences between groups, Mann Whitney U test was used for continuous variables. Fischer's Exact test and Chi-squared test were used to test differences in categorical variables.

Time to RTW was graphically presented with Kaplan-Meier curves in paper I and III. In paper I and in the result section of this thesis, non-parametric comparisons of time to RTW were made by the Log Rank test. Censoring due to death during the study period violates the non-informative-censoring assumption and was therefore treated with a worse-case scenario approach to obtain a more conservative estimate for RTW. This approach means that the participants that died before the event (RTW) was censored at end of follow-up instead of at time of death. In paper I, another cause of censoring was old-age retirement. The participants that turned 65 years before RTW were censored at time of old-age retirement.

Predictive regression analyses were used in all the papers. In paper I predictors of no-RTW were analysed, while predictors of RTW were presented in paper II and III. In the results section of this thesis, however, the results from paper I were recalculated and presented as predictors of RTW to enable comparison between papers. A selection of predictors of RTW from the papers were presented in a forest plot in the thesis. The independent variables were chosen based on clinical and theoretical relevance. Binary logistic regression investigated potential predictors of RTW or no-RTW at a fixed time point and was presented with odds ratio (OR) along with their 95 % confidence interval (CI), and p-values. In paper IV, RTW within 1 year was instead analysed as potential predictor of improvement in general health, pain, and depression between 1 and 5 years post-stroke. Crosstabulations between independent variables and the dependent variable were performed to ensure the sample size for the regression analysis. Spearman's correlation test was used to test the potential multi-collinearity between the independent variables. To test the goodness-of-fit and accuracy of the models, Hosmer and Lemeshow test, Nagelkerke R^2, and Receiver Operating Characteristics (ROC) curves were performed.

Cox proportional hazards regression was used in paper I and III to analyse prediction of time to RTW and presented with hazard ratio (HR) along with their 95 % CI, and p-value. To check for serious violation against the proportional-hazards assumption, Kaplan-

Meier curves and log(-log(survival curves)) were used. If a variable did not fulfil the assumptions, it was adjusted for by stratification in the regression model instead of using it as an independent variable.

Change over time in different aspects of health was investigated in paper IV using shift analyses. Bar graphs graphically presented, and the Wilcoxon signed rank test statistically analysed potential change. In the thesis, Sankey diagrams were used to present change over time at an individual level.

Ethical considerations

Ethical approvals by the Regional Ethical Review Board in Gothenburg are available for all the papers:

- Paper I: Dnr225-08, T801-10, Dnr400-13, T830-15
- Paper II: Dnr042-11, T392-17, T966-17, T540-18
- Paper III: Dnr922-17
- Paper IV: Dnr922-17

Registry-based research is an exception from the general rule of informed consent (95). For instance, data that are handled within the frame of national quality registries are waived from informed consent since it enables improvement of the quality of care and treatment, which is of general interest. This is stated in e.g. GDPR and its applicability is tested by the ethical review board (95, 117). Therefore, no consent was obtained from participants in the present studies. The information about registration in the Riksstroke registry includes information about the fact that the data can be used for research and that the participant can withdraw their information from the registry at any time (118). Hence, the Riksstroke uses an opt-out methodology when including people in the registry. All participation in the questionnaire surveys were voluntary.

The personal identification number was used to link data from different registries and databases. After the pooling, the data were however stored and analysed anonymised or psudonymised and presented in an anonymously way. The risk of identification of any of the participants is very low as the population is registry based.

There is, however, no direct benefit with this research for the participants except for the possibility of improving the situation for future patients. For example, if the data suggests that a participant is not feeling well, there is no possibility of helping the person to get well within the present studies. The research in this thesis focus on a societal level rather than on an individual level. The research has been deemed to provide greater benefit than risk, and results from the screening and registration in the present databases and registries have been used in the clinical setting at the hospitals.

RESULTS

Participants' characteristics

The inclusion of participants is detailed in each paper: Fig 1, paper I; figure 1, paper II; figure 1, paper III; figure 1, paper IV. A summary of the overall inclusion can be seen in figure 3. Drop-out analyses were performed in all of the papers, and no significant difference could be seen between the groups in most of the cohorts regarding a variety of variables (sex, age, stroke severity, stroke type, educational level, and RTW status). In paper III however, the excluded people were significantly older than the included ones, and the participants not answering the question about self-expectations of RTW had a significantly more severe stroke. In paper IV, the participants answering the questionnaire surveys were significantly older than the non-participants.

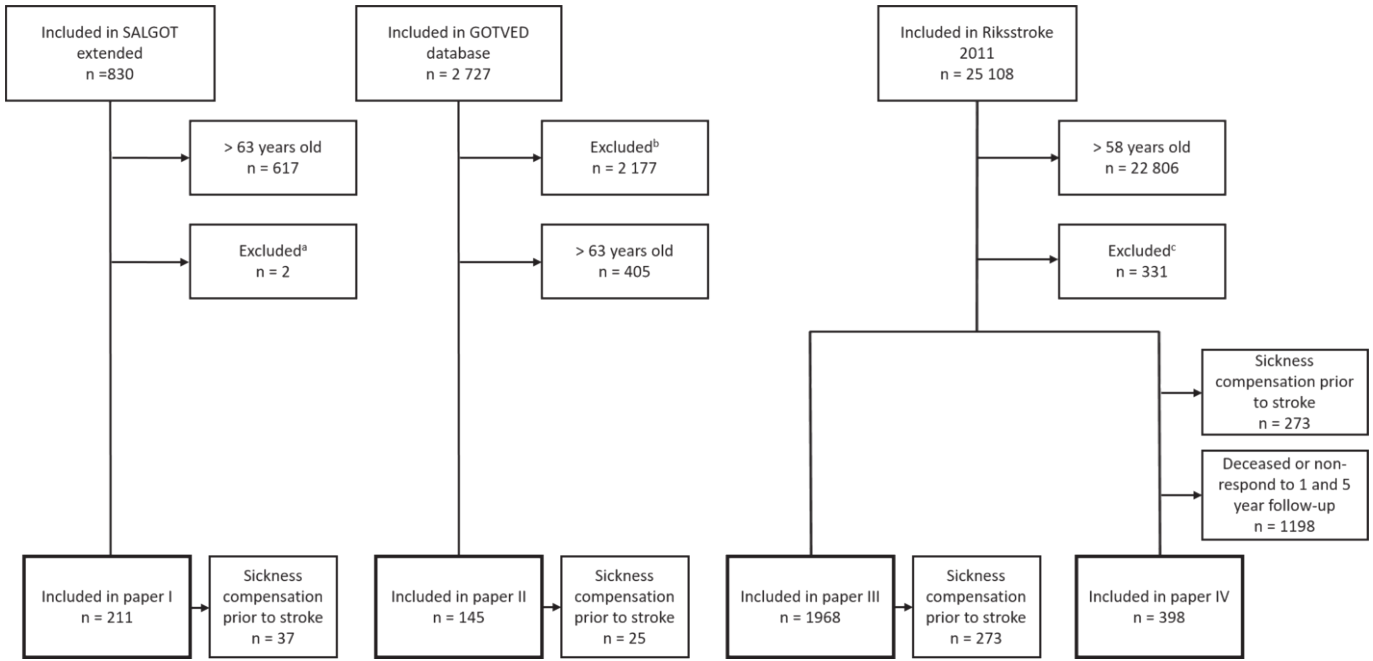

Figure 3. Flowchart of the inclusion of participants in each paper. [a] = Exclusion due to e.g. wrong personal identification number or did not meet the inclusion criteria. [b] = Exclusion due to e.g. duplicate registration, missing clinical assessments, incorrect stroke diagnosis, or previous stroke. [c] = exclusion due to e.g. previous stroke, subarachnoid haemorrhage or living at a nursing home prior to stroke. Abbreviations: SALGOT: Stroke Arm Longitudinal Study at the University of Gothenburg; GOTVED: Gothenburg Very Early Supported Discharge.

The majority of the participants (57-67 %) in all the papers were men, and the mean age at the time of stroke was approximately 50 years (table 4). Around 80 % of the participants were diagnosed with IS and the vast majority had a mild stroke. Some of the participants had absence due to sickness prior to the stroke and 12 % received sickness benefit due to sick leave more than 14 days during the year before stroke. Almost one fifth of the participants included in paper I, II and III received sickness compensation at some extent during the year before they had a stroke.

Table 4. Descriptive characteristics of the study participants in the present papers.

	Paper I	Paper II	Paper III	Paper IV
Participants, n	211	145	1968	398
Sex, n (%)				
Female	69 (33)	62 (43)	716 (36)	135 (34)
Male	142 (67)	83 (57)	1252 (64)	263 (66)
Age, years				
Median (min-max)	53 (21-63)	54 (19-63)	52 (18-58)	53 (19-58)
Mean (SD)	51.1 (9.5)	50.5 (11.0)	49.6 (7.9)	50.4 (7.5)
Stroke type, n (%)				
IS	164 (78)	115 (79)	1608 (82)	331 (83)
ICH	47 (22)	16 (11)	345 (17)	65 (16)
Unknown	0 (0)	14 (10)	15 (1)	2 (1)
Stroke severity				
NIHSS, median (min-max)	1 (0-22)	1 (0-14)	2 (0-42)[a]	2 (0-42)[a]
RLS, n (%)				
Alert			1694 (87)	358 (92)
Drowsy			151 (8)	25 (6)
Unconscious			89 (5)	6 (2)
Sickness absence 1 year prior to stroke, n (%)				
Sickness compensation	37 (18)	25 (17)	331 (17)	Excluded
Sickness benefit (>14 days)	26 (12)	17 (12)		
Hospital stay, days, median (min-max)[b]	6 (1-100)	7 (3-34)	6 (0-100)	6 (0-100)
Reperfusion treatment for IS, n (%)	22 (13)	22 (21)	278 (17)	57 (17)

[a] = approximately 50 % missing data. [b] = 100 days was the maximum days reported. Abbreviations: SD: standard deviations; IS: ischemic stroke; ICH: intracerebral haemorrhage; NIHSS: National Institutes of Health Stroke Scale; RLS: Reaction Level Scale.

Returning to work after stroke – timeframe and frequency

The time to RTW was first investigated in a regional cohort in Gothenburg in paper I, and then in a comprehensive national population in paper III. In the first paper, the RTW (defined as RTW on full-time) continued until just over 3 years post-stroke (figure 4). Most of the RTW occurred within a relatively short period of time after stroke, as the first quartile that RTW did so within 2.7 months, and the second quartile within 12.7 months.

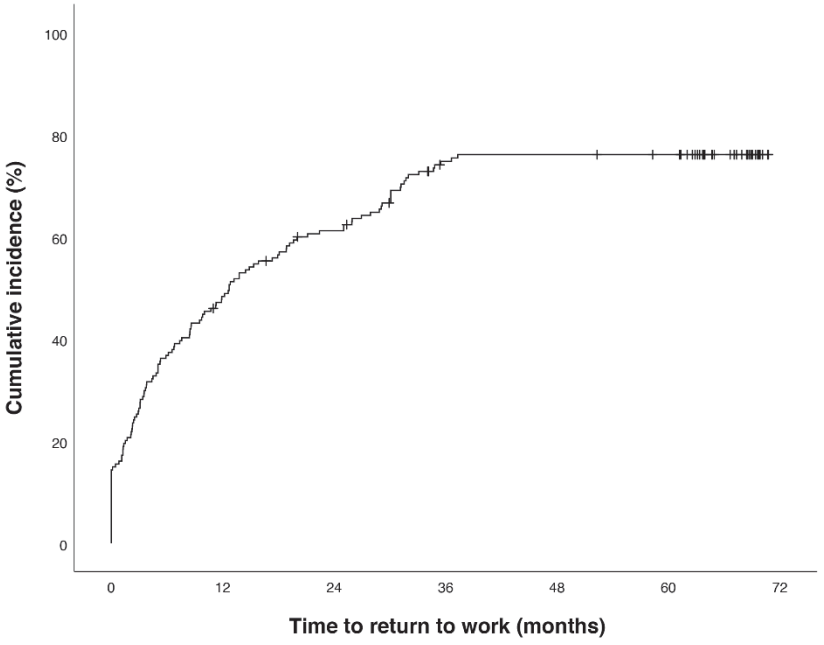

Figure 4. Kaplan-Meier curve of time to return to work after stroke in paper I.

In paper III, the RTW (defined as RTW for at least 50 %) continued beyond 4 years post-stroke (figure 5). Consistent with the findings in paper I, most of the participants RTW quite fast and 48 % had RTW after the first 3 months post-stroke. Within the first year, the numbers of those who RTW were 72 %, and 79 % had RTW within the first

2 years. The men had a significantly faster and higher RTW rate compared to the women (p = 0.010).

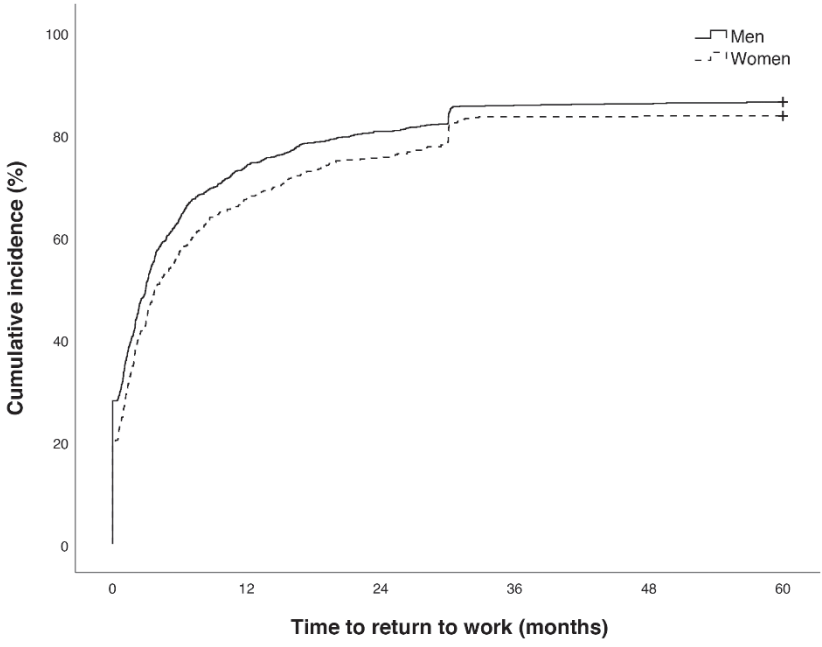

Figure 5. Kaplan-Meier curve of time to return to work after a stroke in paper IV, divided according to sex.

The RTW frequencies from the papers included in this thesis can be seen in table 5. A total of 75-89 % of the participants RTW (partial or full RTW) in the follow-up times of 5-6 years. In the shorter follow-up periods (6-18 months) 37-76 % partially or fully RTW.

Table 5. Frequency of RTW in the individual papers.

	RTW frequency	Amount of RTW	Follow-up time
Paper I	75 %	Full-time	6 years
Paper II	37 %	Full-time	6 months
	65 %	Full-time	18 months
	58 %	Part/full time (≥ 50 %)	6 months
	76 %	Part/full time (≥ 50 %)	18 months
Paper III	85 %	Part/full time (≥ 50 %)	5 years
Paper IV	75 %	Part/full time (≥ 50 %)	1 year
	89 %	Part/full time (≥ 50 %)	5 years

Abbreviations: RTW: return to work.

Predictors of return to work

Prediction of RTW have been analysed in paper I, II and III with minor methodological variations. A selection of the different predictors of RTW in the papers are presented with their OR or HR and 95 % CI in figure 6.

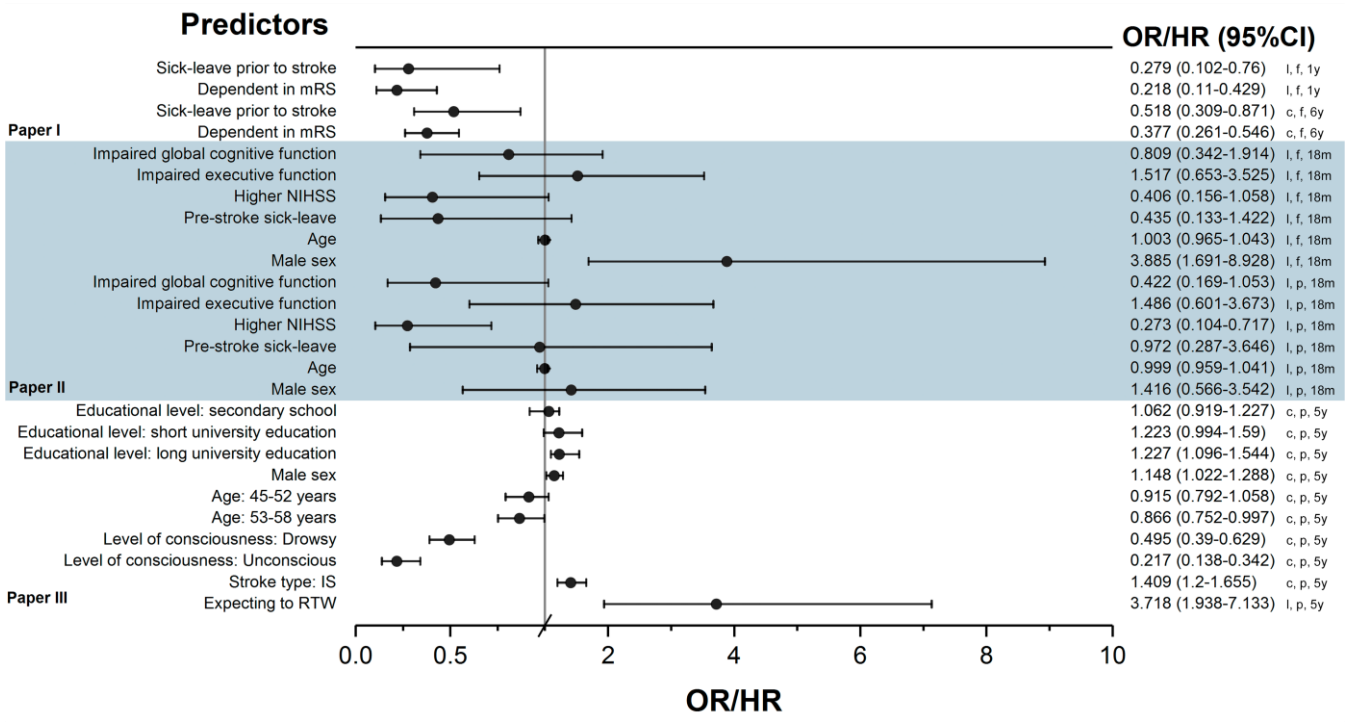

Figure 6. A selection of predictors of RTW in paper I, II, and III. [c] = Cox regression, [l] = logistic regression. [f] = full RTW, [p] = partial RTW. [1y] = 1 year follow-up, [18m] = 18 months follow-up, [5y] = 5 year follow-up, [6y] = 6 year follow-up. Abbreviations: OR: odds ratio; HR: hazard ratio; CI: confidence interval; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; IS: ischemic stroke; RTW: return to work.

Participants with IS had higher odds of RTW compared to ICH in paper III. Stroke severity (assessed with NIHSS or RLS) was perhaps the most consistently significant predictor, as participants with more severe stroke had lower odds of RTW in paper II and III. Furthermore, participants that were functionally dependent at discharge from hospital (assessed with the mRS) had lower odds of RTW in paper I compared to functionally independent participants. Neither screening of global cognitive function, nor executive function, very early after stroke (using the MoCA) did significantly predict RTW in any of the analyses in paper II.

Demographical factors such as sex and age were quite consistent predictors, and the majority of the results showed that male sex and younger age were favourable for higher odds of RTW. Being on sick leave prior to stroke was significant in some of the analyses. The participants that were on sick leave for more than 14 days in a row the year before the stroke had lower odds of RTW after the stroke.

Socioeconomic factors were included in paper III, and a higher educational level (long university education compared to primary school) significantly predicted RTW. Country of birth and income were not included in the regression model since they did not fulfil the proportional hazard assumption, due to different factors being favourable in different time periods post-stroke (Figure 3, paper III). Within the first year post-stroke, the lowest income tertile had the highest RTW, but after the first year, there was a higher level of RTW among the participants with the highest income tertile . Being born outside of Europe was favourable for RTW the first year after stroke. After that, the difference was not so clear except that the lowest level of RTW was seen in the participants born in a European country outside of the Nordic countries within the whole follow-up period. The participants born outside of Europe had a significantly higher educational level compared to the participants born in Sweden ($p = 0.015$).

The participants that had not RTW the first year, but expected to RTW in the future had higher odds of actually RTW within 5 years, compared to the participants not expecting to RTW. Both the crude OR, and the OR adjusted for age, sex, and stroke severity were significant (Table 3, paper III).

Additional results based on the data from paper III are presented in table 6. The results show that in women, only stroke severity was a significant predictor of RTW within 5 years. In men however, stroke type and educational level were also significant determinants.

Table 6. Sex divided Cox regression of predictors of time to RTW, adjusted for country of birth and income.

	Men		Women	
Predictors	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Educational level			Full-time	6 years
Primary school, ref		**0.001**		0.849
Socondary school	1.12 (0.94-1.33)	0.224	0.93 (0.72-1.20)	0.578
Short university education	1.32 (1.01-1.73)	0.044	1.12 (0.67-1.88)	0.655
Long university education	1.51 (1.22-1.88)	**<0.001**	0.95 (0.71-1.27)	0.722
Age				
18-44 years, ref		0.254		0.354
45-52 years	0.93 (0.77-1.11)	0.408	0.87 (0.68-1.11)	0.269
53-58 years	0.86 (0.72-1.03)	0.103	0.84 (0.66-1.07)	0.162
Stroke severity				
Alert, ref		**<0.001**		**<0.001**
Drowsy	0.44 (0.32-0.60)	**<0.001**	0.59 (0.40-0.88)	**0.010**
Unconsiuous	0.21 (0.12-0.38)	**<0.001**	0.22 (0.11-0.46)	**<0.001**
Stroke type, IS	1.49 (1.23-1.81)	**<0.001**	1.29 (0.96-1.73)	0.096

Abbreviations: HR: hazard ratio; CI: confidence interval; IS: ischemic stroke.

The effect of return to work on self-reported outcomes

The participants that had RTW within the first year after stroke in paper IV reported better general health, having less pain, and less depression at 1 year post-stroke, compared to the participants that had not RTW. At 5 years post-stroke, the RTW group still reported better general health, less pain, and less depression than the no-RTW group. However, there were a significant decline in general health and increased pain between 1 and 5 years in the RTW group. In the no-RTW group, there were no significant change between 1 and 5 years post-stroke. To RTW within 1 year also meant significantly lower odds of improvement between 1 and 5 years regarding general

health and pain, but not for depression. Figure 7, 8, and 9 present the individual change in self-perceived general health, pain, and depression between 1 and 5 years post-stroke in the RTW and no-RTW groups. In the RTW group at 1 year, some participants went from reporting the best level at 1 year to the worst level at 5 years in all the three aspects of health, while no one reported that kind of deterioration in the no-RTW group.

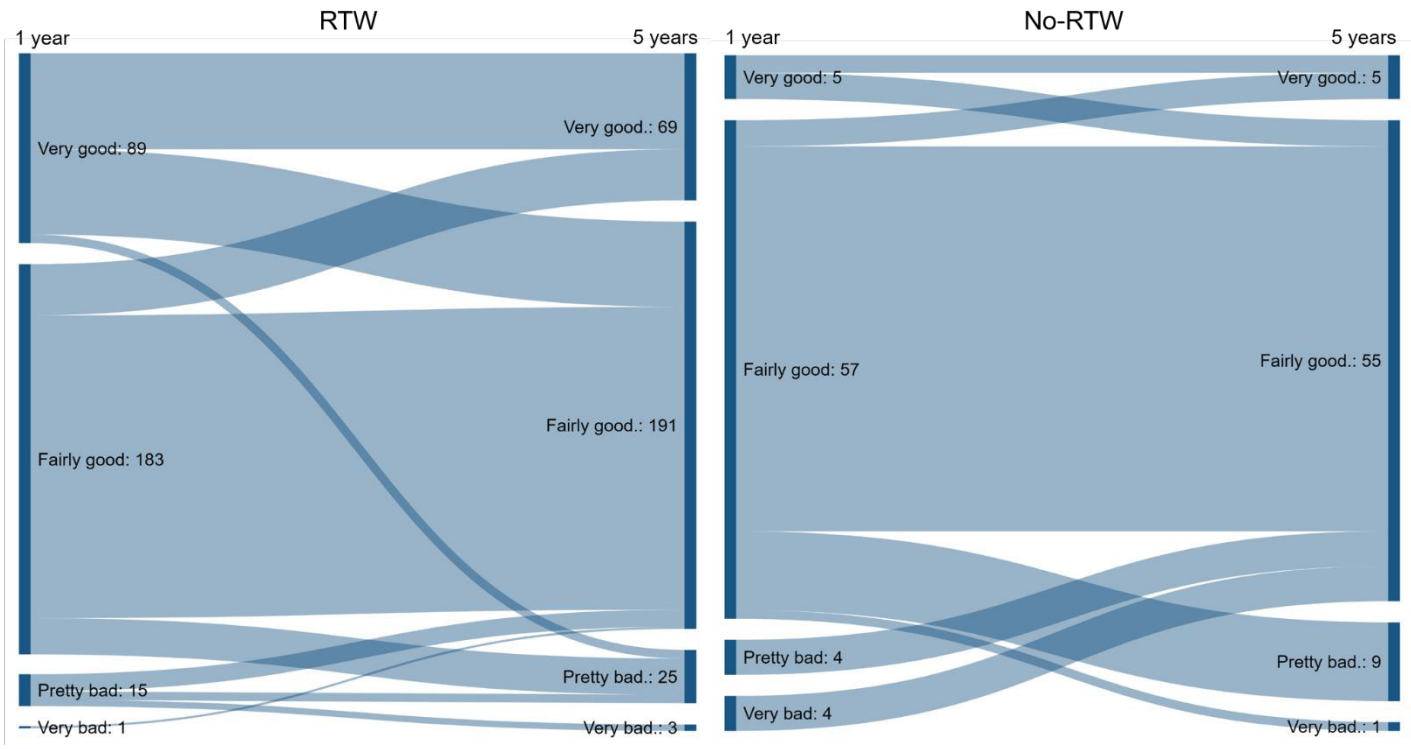

Figure 7. Change in self-perceived general health between 1 and 5 years post-stroke in the RTW and no-RTW groups.

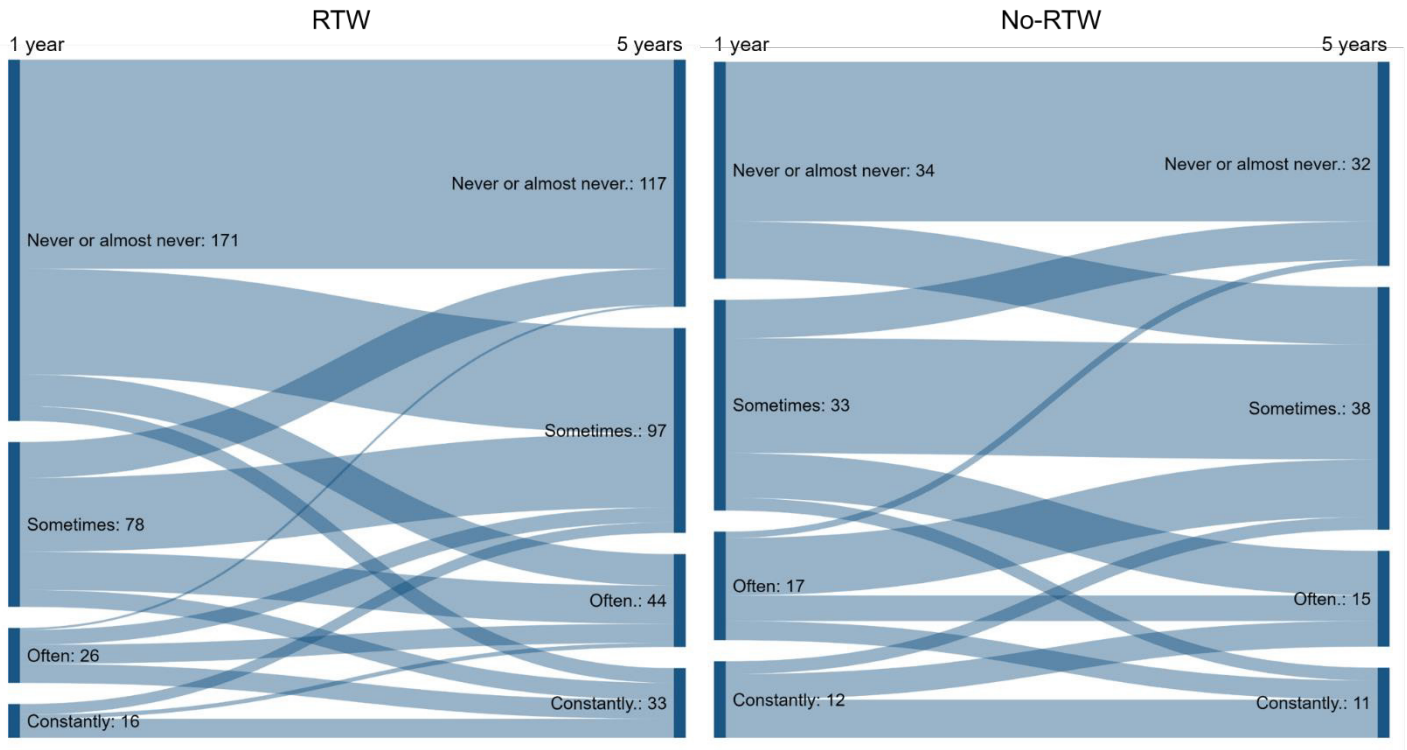

Figure 8. Change in self-perceived pain between 1 and 5 years post-stroke in the RTW and no-RTW groups.

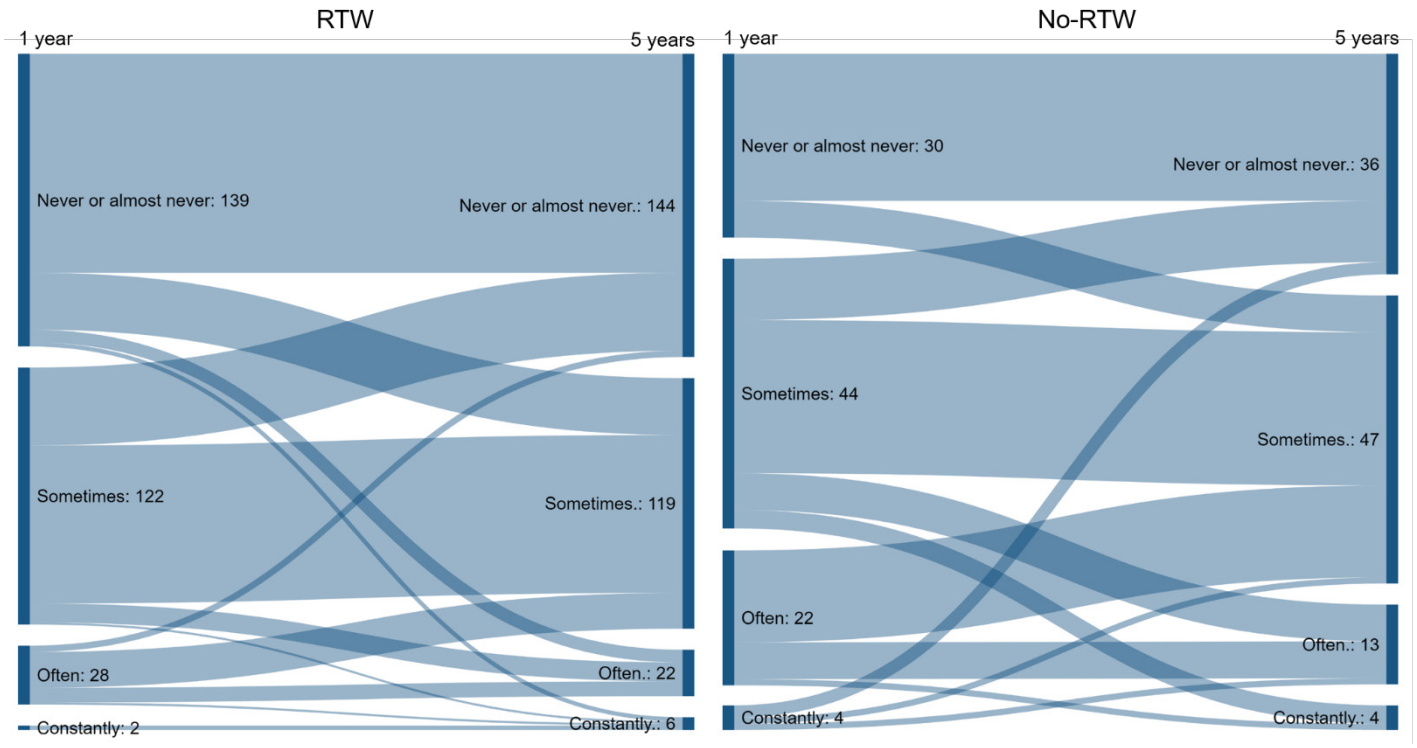

Figure 9. Change in self-perceived depression between 1 and 5 years post-stroke in the RTW and no-RTW groups.

Health-related quality of life was assessed with the EQ-5D 5 years post-stroke in paper I. The index value calculated from the EQ-5D scores showed no significant difference between the participants that had RTW and the participants that had not RTW during the study period ($p = 0.061$). However, the participants that had RTW rated a higher health-related quality of life in the EQ-5D VAS-scale compared to the no-RTW group ($p = 0.012$).

DISCUSSION

Summary of key results

This thesis showed that the majority of the participants at working age did RTW after a stroke. The incidence of RTW were highest shortly after stroke and decreased over time post-stroke. Accordingly, most of the participants RTW within the first 1-2 years after stroke. However, the RTW did continue until 3-4 years post-stroke. Determinants of RTW were sick leave prior to stroke, self-expectations of RTW, demographical, socioeconomic, and stroke-related factors. Cognitive function, though, screened for very early after stroke could not significantly predict RTW. The participants that were in the RTW group at 1 year post-stroke had a better self-perceived general health and less symptoms of pain and depression both at 1 year and 5 years post-stroke, compared to the participants who did not RTW within the first year. However, there was a significant deterioration in general health and increased pain between 1 and 5 years in the RTW group, while no significant change was found in the no-RTW group.

Time to return to work

As described in the introduction, national guidelines of sickness absence after stroke from the National Board of Health and Welfare recommend sick leave on full-time up to 2 months (6). However, the results from paper I and III show that the RTW continue for several years post-stroke. Still, it has to be emphasised that the vast majority that RTW did so within the first 1-2 years. The information that RTW could be a lengthy process after stroke is yet important not only for health-care professionals working with rehabilitation but also for the Social Insurance Agency and policy makers in Sweden. Reasonable expectations and accurate rehabilitation efforts could contribute to an optimised RTW process. The importance of including the time aspect in RTW research has been highlighted before, but there is up until today a lack of studies investigating the time aspect of RTW

(64). Whether the present findings are applicable also in different settings and countries remains unclear. A Finish study has cross-sectionally shown that time also could have an adverse effect on work ability, as approximately 20 % of the participants that had RTW at 1 year, were not working at 5 years post IS (119). The results from a Dutch study are in line with this, which found that a longer time since stroke was a risk factor for unemployment (120). The present thesis did not investigate the aspect of work stability, which refers to if the people able to RTW can continue to work in the long-term.

Return to work frequency

In the present thesis, the frequency of RTW differed somewhat between the papers with different follow-up times and definitions of RTW (full-time or part-time). At least 3 out of 4 participants did RTW within 5-6 years post-stroke and 37-76 % within 6-18 months. Compared to previous research, where the RTW rates also vary substantially (64-66), the current papers present among the highest frequencies. Different follow-up times and RTW definitions could have affected the results. In addition to this, differences in health-care systems and social insurance systems are likely to affect the RTW (121). Furthermore, different views and definitions of work and sickness between countries might influence the RTW rates as well. In Sweden, work is an important part of the identity of a person and it is expected that most working age people do work for a living.

Predictors of return to work

Stroke-related factors

Several factors are important in determining likelihood of RTW after a stroke. One of the most commonly reported factors is stroke severity (64-66, 97), and this is consistent with the present papers where higher stroke severity gives lower odds of RTW. Related paper iii additionally shows a similar pattern in subarachnoid haemorrhages, where those with higher stroke severity (level of

consciousness) at admission to hospital and functional independency at discharge were deemed to regain higher working capacity than those with more severe deficits. It is not surprising that the impact of stroke in the acute phase continue to affect the person in the long-term. Neither is it surprising that work ability is associated with stroke-related factors, which is something that has been emphasised in qualitative studies (122).

It has been discussed in previous research that cognitive problems can be missed when measuring functional dependency (123, 124) and therefore more targeted assessments of cognitive function are important to capture all the aspects of functioning after stroke. Higher cognitive function has been associated with RTW in previous research (72-74), and one study has shown that cognition assessed early (8 days) after stroke could predict RTW (75). In times of shortened hospital stay, paper II aimed at investigating if screening of cognitive function very early after stroke (within 36-48 hours) could predict RTW. However, neither global cognitive function nor executive function separately were significantly associated with RTW. Perhaps the timing of the cognitive assessment was not right, being too early after stroke, or a more detailed testing than the use of MoCA could have resulted in different findings. Nevertheless, follow-up of cognitive function has to be considered in the people being discharged early after stroke, since it has been found important for RTW. Paper II indicates that it is insufficient to only screen for cognition very early after stroke.

In paper III, stroke type was a significant predictor of RTW, with IS being favourable over ICH. This has been shown before (84, 125) and is perhaps related to the fact that people with ICH could have a worse functional outcome than IS (126).

Demographical factors

As for demographical factors, male sex was associated with RTW in paper II and III. This is in line with most previous research (64, 66) and could be because of different societal expectations to be the primary source of income or to take social responsibility in men versus women (64). Furthermore, differences in stroke characteristics and care could be another explanation. Women seem

to have a worse outcome after stroke compared to men (127, 128), mostly explained by age, stroke severity and pre-stroke dependency (127). Furthermore, in some parts of the world, women receive less interventions and treatments then men (128). Women are also under-represented in stroke research (128), which might lead to non-optimised care and hence non-optimised RTW after stroke. In related paper i, functional dependency was the only significant predictor of RTW in women, while socioeconomic and work-related factors were additionally important in men. Similar pattern could be seen in the additional sex-stratified results in this thesis that were based on the data from paper III. Stroke severity was the only significant determinant in women, while also other factors were important for men. It seems as men have higher chances of overcoming stroke-related impairments, depending on other factors, than women. Previous research has also shown that women with illness-restricted activity before stroke had lower odds of RTW than men with illness-restricted activity (70). Different demands in typical female-dominated occupations and male-dominated occupations could perhaps explain a part of the sex differences in RTW as discussed in related paper i, even if this is not a well-established finding in research.

Paper III also presented that people aged 53-58 years had lower odds of RTW than people aged 18-44 years. Age is not a well-established predictor of RTW, as some previous studies present non-significant results (67), some results where people of younger age are less likely to RTW (129), and some where younger people are more likely to RTW (79, 130).

Socioeconomic factors

Paper III investigated the impact of socioeconomic factors on RTW and showed that people with a long university education had higher odds of faster RTW than people with primary school as educational level. Related paper i had contrary results, where higher educational level gave lower odds of RTW, at least in the male population. In women, the variable was non-significant. The reason for the contradictory results is unclear, and previous research also has mixed results showing both higher educational level (81) and lower educational level (74) being favourable for RTW.

Income and country of birth proved to be time-dependent factors and therefore violating the assumptions of cox regression, why their relation to RTW only were graphically analysed. The participants with lowest income had highest RTW the first time after stroke, and the participants with highest income had the overall highest RTW. Perhaps different financial conditions influence the opportunity to be absent from work. Related paper iv also showed that people in the lowest income quartile had significantly less absence from work the first 2 years after stroke compared to people with higher income and discussed their financial dependency as a possible explanation. Furthermore, the work environment and possibility of adaptation at work may differ between low- and high-income occupations and play a role in explaining these results. Previous research mainly present higher income as a favourable predictor of RTW (81, 129). Since paper III investigated prediction of RTW in relation to time after stroke, it indicates that the picture might be more complex than previously shown. The situation for different people is differing depending on time period after stroke.

There are similar results in country of birth, where countries outside of Europe had the highest RTW the first time after stroke (paper III). After that, Sweden, the Nordic countries and countries outside of Europe all ended up with the highest RTW rates within the whole follow-up period, leaving the European countries (outside of the Nordic) with the lowest RTW at end of follow up. A Swedish study not including the time factor, found that people born in Sweden or the Nordic countries were more likely to RTW than people born outside of the Nordic countries (129). In paper III, an explanation for the high RTW rate within the group born outside of Europe could be that they had higher educational level compared to participants born in Sweden.

To be on sick leave for more than 2 weeks the year prior to stroke, regardless of disease causing the absence from work, was a significant barrier of RTW (paper I and II). Similar findings has been present in people with traumatic brain injuries in a previous Swedish study (131).

Self-expectations of return to work

In paper III, the importance of self-expectations of RTW was investigated. Of the participants that had not RTW the first year, the group that expected to RTW had more than 3-fold higher odds of actually RTW within 5 years post-stroke, compared to the people not expecting to RTW. Similar results have been shown for RTW after musculoskeletal diseases (132), but has not been shown for stroke before, to the best of our knowledge. Several modifiable factors (e.g. sense of self, the work context, and disability management) are important when creating expectations of RTW, which gives an opportunity for rehabilitation interventions.

Work-related factors

Except for the predictors mentioned above, the work-environment that the individual should return to is probably of importance as well. Therefore, work-related predictors of RTW were analysed in related paper i. It found that the occupational qualification level and size of the organisation where the participants were employed are important.

To be working in a qualified occupation, often called white-collar worker in previous studies, was favourable for RTW. This is in line with previous results (71, 76, 130). Not surprisingly, if the functional consequences of a disease overlap with the functional demands from the workplace, the likelihood of RTW is lower (133). Related paper i presented lowest RTW rates in "administration and customer service clerks/Service, care and shop sales workers", while a Japanese study had lowest RTW rates in "armed forces occupations", "elementary occupations", and "plant or machinery operators and assemblers" (88). This indicates global differences, even if both studies had highest RTW rates in managers and occupations with high qualifications.

Furthermore, related paper i presented that it is favourable for RTW to be employed in a large organisation, which also has been shown in a Danish study (87). Perhaps larger organisations have more resources and experience to customise the work tasks to help the individual back to work compared to smaller organisations.

However, a person can also be seen as easily replaceable in a large organisation compared to small workplaces.

Other factors

Additional factors potentially affecting RTW not investigated in the present papers, include for instance support from others and personality factors (134, 135). Inaccurate healthcare and rehabilitation after stroke have also been described to negatively affect the RTW process, in previous qualitative research (122). Furthermore, a collaboration between the healthcare and employers are emphasised for enabling RTW (122). Conclusions from qualitative research are that factors affecting RTW are complex, and is an issue needing attention (122, 134).

The effect of return to work on self-reported outcomes

As expected, the self-perceived general health, depression, and pain were better both at 1 year and 5 years post-stroke in the people that had RTW within 1 year compared to people that had not RTW (paper IV). An explanation could be that work is beneficial for health, as discussed in previous research (51, 53), but perhaps also that people with less sequelae from stroke are more likely to both RTW and experience better health, less depression, and less pain. However, there was a significant deterioration in general health and pain between 1 and 5 years post-stroke in the group that had RTW within 1 year. Furthermore, RTW at 1 year significantly predicted worsening in general health and more pain between 1 and 5 years post-stroke. It could be explained by the small decline in function after the initial recovery post-stroke that has been shown in previous research (26-28). However, there was no significant deterioration in the group that had not RTW, suggesting that RTW might not only be beneficial for health. To work despite sickness (sickness presenteeism) has been related to worse health and, for instance, depression and pain (57, 58, 136, 137) and it could be speculated whether sickness presenteeism can be applied to some of the people in the RTW group in the present study. Furthermore, sickness

presenteeism is associated with future sickness absence (58). An interview study, based on the same study population as in paper I, discovered that most of the participants that had RTW and were working several years post-stroke, still were restricted due to the stroke (92). This suggests that sickness presenteeism exists in this group. Furthermore, perhaps the people able to RTW have less continued contact and follow-up with the healthcare. As lack of follow-up has been shown to negatively affect well-being (138, 139), this could negatively affect their health in the long-term.

Paper I presented a slight association between RTW and health-related quality of life, which has been shown before (4, 88). In related paper ii, successful RTW predicted high self-perceived participation and autonomy in all analysed domains (autonomy indoors, family role, autonomy outdoors, and social life and relationships). These findings emphasise the importance of optimising RTW after stroke. However, to avoid a reverse effect on health, the RTW process has to be individualised with considerations to the individual's needs.

Discussion regarding study populations

Most of the participants (57-67 %) in all four papers were men. This is slightly higher compared to the general stroke population in Sweden in 2011 where 52 % were men (140) and could be due to the young age of the participants in the present papers. Men suffer from a stroke at a younger age than women (141); in 2011 for example, the mean age for male stroke patients in Sweden were 73 years and for women 78 years (140). About 80 % had an IS in the present papers and 11-22 % had an ICH. In the general stroke population in Sweden in 2011, the corresponding numbers were 85 % IS and 12 % ICH (140). The majority had a very mild stroke in the papers in this thesis, which is in line with the general stroke population in Sweden in which 82 % had the highest level of consciousness (alert, RLS 1) at admission to hospital in 2011 (140). In paper I and II, the participants had to be treated at a stroke unit (or intensive care unit or neurosurgical unit in paper I) to be able to be included, and 82 % of the stroke patients were admitted to a stroke unit or intensive care unit in all of Sweden in 2011 (140). The median length of hospital stay at the acute ward (mainly stroke unit) was 6-7 days in the

present papers, whereas the hospital stay at the stroke unit was 12 days in the general stroke population in 2011 (140). The study participants had absence due to sickness during the year before the stroke, and between 17 % and 18 % received sickness compensation to some extent prior to stroke in paper I, II and III. For comparison, the same number for the general Swedish working age (15-65 years) population in 2010 was 6.8 % (142). The percentage of participants that received sickness benefit (due to sick leave > 14 days) in paper I and II was 12 %, compared with 9 % of the general working population in Sweden in 2010 (143).

Methodological considerations and limitations

The use of registry-based data with high coverage-rates enables a comprehensive inclusion of people that limits the risk of selection bias, which means selection of participants that gives a study population non-representative of the population intended to study. Furthermore, it entails the possibility of retrieving exact data of for instance number of days on sick leave, when avoiding inaccurate self-reported data. In research however, it is often important with a combination of methods to capture different perspectives of an issue. The use of qualitative methods broadens the picture and highlights the study participants' own subjective experience. This thesis solely used quantitative methods, but to interpret the present results in the light of previous research using for example qualitative methods, gives a higher understanding of the research field.

Even if the use of registry data lowers the risk of selection bias, there has been a considerable drop out in some parts of the papers included in this thesis. Especially the use of follow-up questionnaires has entailed some drop out. Drop out analyses were performed when applicable and did not indicate that the participants were clearly unrepresentative of the larger population. There were however some differences between the participants and non-participants. In the general population, younger people have a tendency to have a lower response rate to questionnaire surveys than older people (144). This is in line with findings in paper IV were the responders were significantly older than the non-responders and could perhaps

explain some of the lower response rates in the present thesis only including people in working age.

The risk of information bias and recall bias has to be considered when working with registry-based data and follow-up questionnaires. For the data to be reliable, it is important that different reporting sources (e.g. healthcare professionals or patients) interpret the indicators and questions in a similar way. To enhance the reliability of the registration, there were instructions to follow for all reporting in the present papers and thesis. For instance, Riksstroke provide guidelines of how to register in the registry at both the acute phase and follow-up (145, 146).

The unique personal identification number forms the basis for comprehensive registry-based research in Sweden. Most registries have clear guidelines on how to handle these identification numbers and usually only anonymised or psudonymised data are sent to the researchers. For instance, in paper III and IV, the code key for each participant were stored at the National Board of Health and Welfare. The personal identification number not only gives opportunities but could also entail a risk since sensitive data are often handled in research. It is therefore important to highlight that the present papers follow the regulations about data handling stated in the GDPR to avoid the risks that comes with working with sensitive data (147).

Three different cohorts consituted the basis for the study populations in the papers. SALGOT in paper I, GOTVED in paper II, and Riksstroke in paper III and IV. There were some overlap between the populations in the papers. All the participants in paper IV were also included in paper III. Furthermore, some of the participants in paper II could also be included in paper III and IV. This is possible since GOTVED included participants having a stroke in May 2011 – April 2016 at Sahlgrenska University Hospital, and Riksstroke populations in paper III and IV included participants having a stroke in 2011 at any hospital in Sweden, which includes Sahlgrenska. Nevertheless, these potentially overlapping participants could only be from 2011 and therefore constitute only a small part of the total study populations. Exact numbers could not be identified due to the anonymized data.

Stroke severity can be measured in different ways. In paper III, stroke severity was not assessed with the commonly used NIHSS,

but with level of consciousness (RLS). The use of RLS as a proxy for stroke severity is not a new approach (110) and is considered as a useful substitute in Riksstroke data where NIHSS is often missing (148-150). In paper I, functional dependency (assessed with the mRS) at discharge was used in the regression model instead of using NIHSS at admission. The mRS has been shown to highly correlate highly with the NIHSS in previous research (151).

The questionnaires used in the papers were not formed specifically to fit the present research questions but were more generally designed to investigate life after stroke. For instance, the question that was used to assess expectations of RTW in paper III was formulated to assess RTW in general after stroke, and this limits the ability to draw conclusions from the results.

RTW has throughout this thesis been defined as absence of sickness benefit or sickness compensation, with the exception if the registration in the Social Insurance Agency ended in the near time of death or old-age retirement (turning 65 years old). Since the Social Insurance Agency is a public authority in Sweden applicable for both employees, self-employees, as well as people on parental leave, their registries are comprehensive. There are however potential limitations with the use of sick leave data as RTW assessment. There is a risk that people end the registration with grants from the Social Insurance Agency without actually RTW (or dying, or old-age retiring), and instead live with financial support from a next of kin, or with social assistance from the Social Services in Sweden. Furthermore, work stability was not considered in the present definition of RTW. Participants that fulfilled the criteria of RTW were considered as RTW even if they returned to sickness absence at a later stage.

Logistic or cox regression analyses were used throughout all the papers. Several different approaches can be used while building the regression models (152, 153). The variables in the present papers were included in the models based on theoretical and clinical relevance. Furthermore, several assumptions had to be fulfilled for the analyses and different methods could be used to test the goodness of fit of the models (152). Spearman's correlation tests, cross tabulations, Kaplan-Meier curves, log(-log(survival curves)), and graphical representation of partial residuals versus survival time were used to

check for fulfilments of assumptions. To test the goodness of fit of the models, Hosmer-Lemeshow tests, Nagelkerke R^2, and ROC curves were performed. Statisticians were consulted in the model building and testing procedure in the papers.

Multiple regression models were performed in paper II, which could entail some problems that need to be discussed. All the models had a clinical or scientific objective. Both global cognitive and executive cognitive function were analysed and had to be inserted into different models due to high correlation between the variables. The outcome RTW was tested at both 6 months and 18 months. The shorter follow-up was to be able to compare the results to the one study that previously had investigated early cognitive function and RTW (75), and the longer follow-up was due to our previous results that RTW continued for a longer time post-stroke. Both full RTW and partial RTW were analysed since full RTW was more comparable to international studies, while also partial RTW are relevant in Sweden. The risk of multiple testing problems (an increased risk of receiving a false significant result, type I error, with multiple testing) have to be considered when performing multiple analyses (154). There are ways to adjust for this risk, for instance adjusting the p-value using the Bonferroni correction. There is however also a risk of false non-significant results (type II error) when controlling for multiple testing, and there is no clear consensus regarding this (155, 156). In paper II, no adjustments for multiple testing were made but no significant results for the main question were obtained either, hence the results are considered reliable.

The present papers did not investigate the impact of rehabilitation or vocational training on RTW. Nor was the type of job the participants returned to considered. Previous qualitative research has presented areas in rehabilitation that are found to be important for RTW (157, 158), but this could also be topics for future research.

Generalisability

Due to the long-term follow-ups in the present papers, the included participants suffered from the stroke several years ago. This could potentially affect the generalisability to patients with stroke today. Stroke care has evolved the last decades and hence the disability and consequences for the affected person.

The results in the thesis are closely connected to the health-care system and social insurance system in Sweden. Both the healthcare and social insurance are tax funded and available to everyone. This limits the generalisability of the results to other countries with different systems. The generalisability within Sweden and similar countries should however be high since comprehensive study populations that covers people with for example different sociodemographic backgrounds, are used.

CONCLUSION

The majority of people having a stroke in working age do RTW. Most RTW within the first year but the RTW process continue for several years post-stroke. This relatively new finding should be of importance for healthcare professionals and the Social Insurance Agency, to optimise the RTW process.

A variety of factors are associated with higher frequency of RTW or faster RTW. Some are modifiable and some are not, but the knowledge could contribute to more individualised information and rehabilitation efforts to the affected person.

The people that do RTW after a stroke have a better self-perceived health in several aspects. However, to RTW seem to be not only a facilitator of good health but could perhaps rather be a barrier of continued improvement in some cases.

RTW after a stroke in working age is a complex process needing further attention in research, healthcare, and society. The results in this thesis could hopefully emphasise the importance of this subject and contribute to some extent to a more individualised and optimised RTW after a stroke.

FUTURE PERSPECTIVES

- The findings regarding time to RTW could be an aspect to consider for policymakers in forming guidelines for sickness absence after stroke. This, in order to avoid unreasonable pressure to RTW too fast and work despite sickness.
- For healthcare professionals and the Social Insurance Agency, the complexity of RTW and its predictors are important to consider. Different aspects are important for different people in different time periods, and individualised care and handling should be beneficial.
- More research is needed in this field. Registry based studies in combination with qualitative methods could hopefully bring more clarity into this subject.

ACKNOWLEDGEMENT

Det finns många som varit delaktiga i denna avhandling på ett eller annat sätt, och många som stöttat mig längs vägen. Tack!

Jag vill uttrycka min tacksamhet gentemot de deltagare, sjukvårdspersonal, registerhållare och handläggare som tillsammans skapat de register och databaser som legat till grund för denna forskning, ett speciellt tack till de kollegor som varit delaktiga i datainsamlingen till SALGOT och GOTVED. Utan er hade detta bokstavligen inte varit möjligt.

Mitt största tack till mina handledare för ert engagemang och för att ni trott på mig. Ni har varit tillgängliga när jag behövt det oavsett dag eller tid, och ni har fått mig att förstå vad jag klarar av att genomföra. Ni har inspirerat mig med ert driv och er stora kompetens. Min huvudhandledare **Katharina Stibrant Sunnerhagen** för att du visat mig vad forskning innebär och fick mig att påbörja doktorandstudierna. För din otroliga förmåga att se möjligheter när mycket känns hopplöst. Till min bihandledare **Hanna Persson**, tack för din omtänksamhet och klokhet. Ditt tålamod och stora vilja att lära ut har varit ovärderligt. Tack till er båda för att ni uppmuntrat mig att göra det jag vill inom karriären, även när det inneburit annat än forskning. Jag har er som förebilder, inte bara i forskning, utan också som handledare och människor.

Till alla kollegor i forskargruppen för Rehabiliteringsmedicin, speciellt **Lena Rafsten**, **Emma Kjörk**, **Netha Hussain**, **Elisabeth Brodin**, **Margit Alt Murphy**, **Karin Törnbom**, **David Krabbe**, **Charlotta Josefsson**, **Dongni Buvarp**, **Sofi Andersson**, **Lamprini Lili**, **Malin Reinholdsson**, **Tamara Abzhandadze**, **Elisabeth Åkerlund**, och **Adam Viktorisson**. Utan er hade denna resa varit betydligt tråkigare och mer skrämmande. Tack för alla samtal om allt möjligt i livet. Alla skratt och all stöttning har varit ovärderligt. Den hjälpsamhet och omtänksamhet vi har i gruppen är något speciellt som är få förunnat.

Till alla medförfattare, förutom ovan nämnda, även speciellt **Bo Norrving** och **Marie Eriksson**. Tack för att ni på ett uppmuntrande och positivt sätt bidragit med er stora kompetens.

Tack till kollegor i kliniken som inspirerat mig till att vilja utvecklas och bli en bättre läkare i alla avseenden. Tack till AT-kansliet på Sahlgrenska Universitessjukhuset, och speciellt min AT-chef **Erik Hulegårdh**, för att ni anställde mig som forskar-AT-läkare och varit flexibla och uppmuntrande i balansen mellan klinik och forskning.

Till alla vänner och familj för att ni alltid stöttat och uppmuntrat. Ni har hjälpt mig vara i nuet och fokusera på det viktiga. Utan er hade dessa år varit oändligt mycket tråkigare. Speciellt tack till **mamma**, **pappa**, **Cecilia**, **Polly** och **Lo**.

Till sist, tack **Robin**. Din uppmuntran var stor del i att jag vågade påbörja detta. Hur frustrerande det än varit att du inte kunnat se problemen jag målat upp, så har din förmåga att se möjligheterna och inte ta så allvarligt på saker varit viktig för mig. Ditt stöd betyder allt.

This thesis was founded by grants from the Swedish Research Council (VR2012-3523 and VR2017-00946), the Swedish Heart and Lung Foundation, the Swedish state under the agreement between the Swedish government and the county councils - the ALF agreement (ALFGBG-718711 and 73750), the Norrbacka-Eugenia Foundation, the Swedish Brain Foundation, the Health & Medical Care Committee of the Regional Executive Board – Region Västra Götaland, King Gustaf V's and Queen Victoria's Freemasons' Foundation, Agneta Pruyz-Folke's and Gösta Folke's Foundation, the FRF Foundation, and the Swedish National Stroke Association.

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