Productivity-related cognitive impairments after ischaemic stroke

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Abstract

The global burden of stroke is huge and increasing despite significant improvements in acute stroke care in recent decades. The indirect costs, such as productivity losses due to patients’ inability to return to work after stroke, are a major factor in the accumulation of this burden and are estimated to outweigh the direct costs of stroke.

Post-stroke cognitive impairments seem to relate intimately to functional outcomes and quality of life after stroke, but their role in the creation of stroke-related productivity losses remains uncertain. The aim of this study was threefold: to compare the prevalence and severity of post-stroke cognitive impairments in relation to the severity of clinical neurological impairments; to specify the role of cognitive impairments in patients’ ability to return to work after stroke; and to assess the use of stroke-related income supplements and the role of cognitive impairments in supplement use.

A consecutive cohort of 230 working-aged patients with a first-ever ischaemic stroke was enrolled in two Finnish hospitals. The patients underwent repeated neuropsychological assessments in order to describe their cognitive sequelae. Cognitive data from baseline, six-month and two-year follow-up examinations were analysed in relation to demographic, clinical and occupational information on the patients. Cognitive impairments were defined based on the performance of a healthy demographic control group (N =50).

Cognitive impairments frequently appeared among otherwise intact patients. After taking into account other relevant factors, baseline cognitive impairments most effectively predicted the return to work of the patients six months after the stroke. Regarding the use of stroke-related income supplements, atrial fibrillation was the most effective health-related predictor, and cognitive impairments the most effective stroke-related predictor.

The results of the study emphasize the usefulness of early neuropsychological assessments in treatment planning and the importance of cognitive impairments in the accumulation of post-stroke productivity losses.
Tiivistelmä

Aivoinfarktiin akuutti- ja hintaon johdattu kehitys kuluneiden vuosikymmenten aikana on ollut erittäin merkittävä. Aivoinfarkti on silti yhä yksi yhteiskunnallisesti merkittävimmistä sairauksista siihen liittyvän kuolleisuuden ja vammasuuden vuoksi. Aivoinfarktiin vuoksi menetetään enemmän laatupainotteisia elinvuosia kuin minkään muun sairauden vuoksi. Vaikka kehittyneissä maissa aivoinfarktiin sairastuneista vain joka neljäs on työikäinen, ovat juuri työikäiset yhteiskunnallisesti erityisen merkittävä aivoinfarktipotilasryhmä heihin keskittyvien sairastumisen epäsuorien kustannusten, erityisesti tuottavuuden menetyksien vuoksi.


Tutkittaessa aivoinfarktin aiheuttamia haittoja arjen toimintakyvyssä, elämänlaadussa ja mielivallassa näyttää neuropsykologisilla häiriöillä olevan keskeinen merkitys. Työikäisten potilaiden tuottavuuden muutosten osalta tieto neuropsykologisten häiriöiden merkityksestä on yhä vähäistä.

Tämän työn tavoitteena on kuvata kliinisesti merkittävien neuropsykologisten häiriöiden yleisyttä työikäisillä aivoinfarktipotilailla. Lisäksi tutkimuksessa selvitetään, mikä merkitys neuropsykologisilla häiriöillä on työikäisten potilaiden paluuseen työhön ja aivoinfarktiin liittyvien yhteiskunnallisten etuisuksien käyttöön, huomioiden muut hoidon lopputuloksen vaikutuksen tekijät.


Tutkimus vahvistaa käsitystä varhain toteutetun neuropsykologisen arvioinnin hyödyllisyystä osana aivoinfarktipotilaan akuuttivaiheen moniammatillista toimintakykymuutosten arviota. Tutkimus tarjoaa uutta tietoa neuropsykologisen jälkioireiston yleisyydestä muutoin vähäoireisilla potilailla. Tutkimus perusteella neuropsykologinen jälkioireisto vaikuttaa merkittävästi aivoinfarktinkin epäsuorien kustannusten muodostumiseen.
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List of original publications

This thesis is based on the following original publications, referred to in the text by Roman numerals I-III.


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Abbreviations

CT    Computed Tomography
DF    Degrees of freedom
GCS   Glasgow Coma Scale
ETK   Finnish Centre for Pensions
HR    Hazard ratio
IBM   International Business Machines
KELA  Finnish Social Insurance Institution
M     Mean
MRI   Magnetic Resonance Imaging
mRS   modified Rankin Scale
NIHSS National Institutes of Health Stroke Scale
OR    Odds ratio
POMS  Profile of Mood States
QALY  Quality-adjusted life year
SD    Standard deviation
SPSS  Statistical Package for Social Sciences
WAIS-III Wechsler Adult Intelligence Scale, Third Edition
WMS-R Wechsler Memory Scale Revised
1 Introduction

1.1 The global burden of stroke

Ischaemic stroke refers to a sudden loss of blood circulation to an area of the brain, which results in ischemia, nerve cell death and a corresponding loss of neurological function (Sacco et al., 2013). Broadly, stroke also refers to intracerebral and subarachnoid haemorrhages, but in this presentation, ischemic stroke is intended unless otherwise specified. In 2005, 16 million new strokes occurred worldwide causing almost six million deaths and forcing another five million survivors with their families and communities to cope with permanent disability (Mackay, Mensah, World Health Organization, & Centers for Disease Control and Prevention (U.S.), 2004). In many developed countries, stroke is a leading cause of adult disability and takes more quality-adjusted life-years (QALY) than any other disease. Disability after stroke derives from motor, sensory and cognitive impairments challenging survivors’ physical, psychological and social well-being.

Direct and indirect costs of stroke in Europe in 2010 were estimated at 63 billion euros, and in the US, 74 billion dollars (Gustavsson et al., 2011). By 2030, 23 million new strokes are estimated to occur (Mackay, Mensah, World Health Organization, & Centers for Disease Control and Prevention (U.S.), 2004). Epidemiologically, stroke is in constant change (Feigin et al., 2015). Despite decreasing stroke-related mortality (Koton et al., 2014), absolute numbers of people affected and related deaths are increasing (Feigin et al., 2014) and thereby global stroke burden continues to increase (Feigin et al., 2015). The developing countries bare the heaviest burden of stroke, but even in developed countries there are worrying trends, such as the increasing incidence of stroke in the working-aged population (Kissela et al., 2012; Krishnamurthi et al., 2015). More research is needed to establish a knowledge basis for effective prevention, treatment strategies, and resource allocation.

Large-artery atherosclerosis induced emboli is the leading aetiological cause of ischaemic stroke with the prevalence of 40-60 %, while intra-cranial small-
vessel disease comprises 20-35% of all ischaemic strokes (Aivoinfarkti. Cerebral infarction [stroke]: Current Care Guidelines Abstract, 2011). Cardiac embolism is the third biggest cause of ischaemic stroke with the prevalence of 15-25% (Aivoinfarkti. Cerebral infarction [stroke]: Current Care Guidelines Abstract, 2011). Of strokes with cardiac aetiology, atrial fibrillation is by far the most common cause. Atrial fibrillation is still both under diagnosed and related to more adverse outcomes and therefore of special importance to the prevention and treatment of stroke (Lamassa et al., 2001).

1.2 Cognitive impairments after stroke

Conventionally, the focus in research on post-stroke disability has been on apparent physical deficits, such as loss of functional movement (for a review on motor recovery after stroke, see e.g. Langhorne, Coupar, & Pollock, 2009). Tremendous developments during the past decades in acute stroke care also facilitate attention to less obvious hindrances of recovery. Sometimes called hidden dysfunction (Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009), cognitive impairment after stroke is receiving growing attention, as it seems to relate intimately to stroke outcome.

Cognitive impairments after stroke refer to various brain-derived information-processing impairments, such as deficits of attention and executive function, working memory, learning, calculation, visual perception, processing speed, visual spatial and constructional skills, and language and motor skills. Acute cognitive impairments develop within the first minutes from blood occlusion in the affected brain vessel. Due to changing perfusion conditions, oedema etc., acute phase impairments tend to fluctuate. After the stabilization of the acute phase, the sub-acute phase begins, which is considered to continue up to approximately three to six months after the stroke. According to Gottesman & Hillis (2010) review, more than two third of the patients suffer from cognitive impairments during the sub-acute phase. More recently, Schaapsmeersders et al. (2013) showed that these impairments can be highly persevering – approximately half of 277 stroke survivors aged < 50 years suffered permanent cognitive impairments even a decade after the stroke.
Cohort studies have linked post-stroke cognitive impairments to patients’ long-term cognitive outcome (Nys, van Zandvoort, de Kort, van der Worp et al., 2005), depressive symptoms (Nys et al., 2006) and quality of life (Hochstenbach, Anderson, van Limbeek, & Mulder, 2001; Nys et al., 2006). Regarding functional outcome after stroke, there are two review studies that have focused specifically on cognitive impairments and emphasized cognitive impairments as a determinant of functional outcome after stroke (Barker-Collo & Feigin, 2006; Feigin, Barker-Collo, McNaughton, Brown, & Kerse, 2008). As such, detection of post-stroke cognitive sequelae can be seen as a prerequisite for developing sound rehabilitation strategies.

Post-stroke cognitive impairments can be detected using a clinical neuropsychological assessment. It includes multiple tests and a focused interview covering a wide range of the above-mentioned cognitive functions and their deficits. Several issues must be specifically attended to in a study setting out to create a credible account to measure post-stroke cognitive impairments. Of particular importance are methods of deriving cut-offs for impaired performance, especially whether the cut-offs are grounded on demographically similar control data. In a clinical setting of dealing with acute patients, the timing of a neuropsychological assessment is also relevant to the reliability of the results. Expediting the assessment too much makes the assessment vulnerable to a patient’s fluctuating acute phase conditions, such as delirium, hence jeopardising the reliability of the assessment. Yet gathering all the outcome-related information as early as reliably possible is strongly supported by both basic research evidence on plasticity and clinical evidence of time-dependent effectiveness of stroke rehabilitation (Jenkins & Merzenich, 1987; Kleim & Jones, 2008; Musicco, Emberti, Nappi, Caltagirone, & Italian Multicenter Study on Outcomes of Rehabilitation of Neurological Patients, 2003; Salter et al., 2006). The earlier the assessment, the earlier the information regarding the cognitive impairments can be utilized in the treatment and rehabilitation of a patient. There is some evidence that early cognitive impairment, as occurs in the transition between acute and sub-acute phases of stroke, can reliably predict later outcome. Nys, van Zandvoort, de
Kort, van der Worp et al. (2005) assessed the prognostic value of domain-specific cognitive abilities in 168 patients within three weeks after a first-ever stroke, and concluded that cognitive abilities in the early phase after stroke are excellent independent predictors of long-term cognitive and functional outcome.

The resources required for thorough neuropsychological assessments to evaluate cognitive impairments vary between and within hospitals. Without effective neuropsychological assessments, assumptions of a stroke patient’s cognitive state rely on three types of less time-consuming but more or less insensitive factors. First, a widely-used method to gather information on cognitive state of stroke patients are cognitive screening tools such as Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975), which however cannot be recommended due to insensitivity in the context of stroke patients (Nys, van Zandvoort, de Kort, Jansen et al., 2005). Second, known risk factors for post-stroke cognitive impairments can give a hint of a patient’s cognitive state. For example, an ischemia in left cerebral arteria of a right-handed patient is likely to cause speech problems. Correspondingly an ischemia in right frontoparietal areas associates with left hemispatial neglect. For a more comprehensive review on predictors of cognitive dysfunction resulting from ischaemic stroke, see Gottesman & Hillis (2010). Third, cognitive impairments associate with other measures of stroke severity. In general, the clinically most severe strokes tend to exhibit the most severe cognitive impairments as well. Further research is needed to describe the parallels of clinical neurological and cognitive impairments more specifically. Information on the relationship between clinical stroke severity and the severity of cognitive impairments has important practical implications for the management of stroke patients, both those symptomatic and those with successful recovery.

1.3 Return to work after stroke

Given that three strokes out of four attack patients who are already retired, it is no wonder stroke is often considered a disease of the elderly. Sometimes this curved age distribution seems to mask the one out of four stroke patients who
are in fact working-aged (for Finnish data see Meretoja et al., 2011 and for a more global perspective see e.g. Daniel, Wolfe, Busch, & McKeVitt, 2009). In 2013, almost 7.3 million new ischaemic strokes occurred in 20-64 year-olds worldwide (Krishnamurthi et al., 2015). Despite the less frequent incidence compared to the elderly, this younger stroke subgroup arguably presents a crucial patient group in the total socio-economic burden of stroke. In the core of this argument is the issue of whether the patients can return to work after the stroke.

The socio-economic burden of stroke derives from both direct and indirect costs. The direct costs refer to inpatient stays, outpatient visits, rehabilitation, and medications, whereas the indirect costs refer to, for example, various losses of productivity. Demaerschalk, Hwang, & Leung (2010) conducted a systematic literature review to determine the costs of ischaemic stroke in US and argued that the indirect costs outweigh the direct costs of stroke. Most importantly, it is the working-aged stroke-survivors’ post-stroke inability to return to their former employment that so devastatingly inflates the indirect costs and, hence, the total socio-economic burden of stroke.

Daniel et al. (2009) reviewed systematically the social consequences of stroke for working-aged adults and found that approximately half of the working-aged stroke patients do not return to work after the stroke. In individual studies evaluated in the review, the reported rates of return to work, however, varied between 0-100%. A major cause for the extreme variation in the return to work rates was the way work was defined. In order to enhance repeatability across studies, there is a growing trend of defining work as employment outside the house.

The well-documented, most effective predictor of a stroke patient’s vocational outcome is stroke severity (Daniel et al., 2009; Treger, Shames, Giaquinto, & Ring, 2007). Depending on the study at hand, stroke severity refers to various measures regarding the incident stroke. The most commonly used measures are gross neurological and functional outcomes. The growing cognitive demands of
current working life necessitate a description of the relationship between the
cognitive severity and the vocational outcome of stroke as well.

While stroke severity may be the prevailing factor affecting the outcome of
stroke, it is not the only one. The reasons for stroke patients’ compromised
vocational outcome are multifaceted, and only partially related to the stroke per
se (Howard, Till, Toole, Matthews, & Truscott, 1985). The non-stroke-related
factors constitute from demographic and occupational factors, such as age,
education and occupational status (Howard et al., 1985; Tanaka, Toyonaga, &
Hashimoto, 2011; Treger et al., 2007). For example, older patients are more
unlikely than younger patients to return to work after stroke irrespective of
stroke severity. Similarly, lower education and occupational status both increase
the risk of adverse vocational outcome.

So far, the research conducted regarding the role of cognitive impairments in
the vocational outcome of stroke survivors is sparse and methodically limited.
There are a number of prospective cohort studies assessing post-stroke return to
work, but typically the analysis of cognitive impairments has been either
omitted or restricted to single grave impairments such as aphasia or neglect,
detected in the clinical neurological examination. Most of the studies have not
applied neuropsychological assessments, hence being capable of detecting only
the most severe impairments (Black-Schaffer & Osberg, 1990; Howard et al.,
1985; Hsieh & Lee, 1997; Lindstrom, Roding, & Sundelin, 2009; Neau et al.,
1998; Saeki & Toyonaga, 2010). One study reported defects of intelligence and
memory to affect vocational outcome but without parallel analysis of non-
stroke-related effectors of return to work (Kotila, Waltimo, Niemi, Laaksonen, &
Lempinen, 1984).
1.4 Measuring productivity beyond employment

However well grounded it is in stroke research to measure productivity as work, and work in turn as employment outside the house, this circumscription inevitably fails to appreciate the uncountable forms of human productivity seen in the real world, in the lives of individual stroke survivors. For example, working-aged stroke patients who are unemployed but help with the day-care arrangements of small grandchildren, obtain groceries for elderly parents, or coach a local junior football team arguably are contributing to society despite the lack of pay. Thus, losing the ability to participate in these activities after stroke could be considered a productivity loss. Nonetheless, for a research setting, it is highly challenging to measure variation that is so heterogenic by nature. Arguably, measurement of all types of stroke-related productivity losses, work-related or otherwise, is valuable in understanding the socio-economic burden of stroke. As Joo, George, Fang, & Wang (2014) conclude after reviewing the relevant research literature on indirect costs associated with stroke between years 1990-2012: “…indirect costs account for a significant portion of the economic burden of stroke, and there is a pressing need to develop proper approaches to analyse these costs and to make better use of relevant data sources for such studies or establish new ones.” (p. 1753).

Possible sources for productivity-related information that is not limited to employment are income redistribution programs. In many countries, individuals outside of the workforce receive one or more forms of income supplements, such as disability, sick leave, or unemployment benefits. When stroke-related, these income supplements further raise the negative economic impact of stroke by adding to the societal cost beyond the productivity losses caused solely by the inability to work. However, unlike the inability to work, stroke-related income supplements are not restricted to the employed subpopulation of patients – both employed and those outside the workforce may receive them. As illness-based income supplements are always based on disability, they may capture productivity-related variation. Therefore, income
supplement data can provide a complementary and less well-understood perspective on stroke-related productivity losses.
2 Aims of the study

The purpose of this thesis was to assess the role of cognitive impairment in stroke-related productivity losses in a working-aged sample of patients suffering their first-ever ischaemic stroke.

In the first part (Study I), the relationship between post-stroke cognitive impairments and other neurological impairments was assessed. Specifically, the aim of the first study was to describe the relationship between total National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989) scores and cognitive impairments following stroke. Based on previous studies of neglect and aphasia (Croquelois, Wintermark, Reichhart, Meuli, & Bogousslavsky, 2003; Hillis, Wityk, Barker, Ulatowski, & Jacobs, 2003), it was hypothesized that the NIHSS would be insensitive to other domain-specific cognitive impairments as well. However, the lowest total NIHSS scores were hypothesized to relate to good cognitive outcomes on a global level of cognitive function.

In the second sub study (Study II), the role of cognitive impairments in the vocational outcome of the patients was examined, acknowledging the multifactorial nature of post-stroke return to work. The aim was to investigate how the severity of stroke, defined as the number of cognitive impairments within the first weeks after a first-ever ischaemic stroke, predicts the inability to return to employment within the six-month follow-up. The analysis was adjusted for demographic, vocational and clinical predictors and mood state. Given that gross cognitive impairments are known to predict return-to-work, it was hypothesised that a more sensitive assessment of cognitive impairments would enhance these predictions.

Finally, in the third sub study (Study III), a novel method is introduced to examine productivity-related variation in a stroke cohort. In this study, registry data on stroke-related income supplement use was combined to the clinical patient data in order to trace stroke-related productivity changes of the entire cohort irrespective the premorbid vocational status of the patients. Given the relevance of cognitive impairments to the vocational outcome of stroke, it was
hypothesized that the predictors of income supplement use would be multifactorial and would emphasize the importance of the cognitive impairments.
3 Methods

3.1 Design

A prospective cohort study design was used. Eligible stroke patients were recruited during their acute care from the neurological acute care units and followed up periodically until two years after stroke. The patients underwent repeated neuropsychological assessments in order to describe their cognitive sequelae that was analysed in relation to demographic, clinical and vocational information on the patients. Cognitive impairments were defined based on the performance of a healthy demographic control group.

3.2 Setting

The data were collected consecutively in two Finnish hospitals: Helsinki University Central Hospital, Helsinki and Lapland Central Hospital, Rovaniemi. Recruitment started in April 2007 and finished in October 2009. All patients in this cohort were treated according to the institutional guidelines for stroke care. Demographics, clinical and baseline neuropsychological data were collected within the first weeks after the stroke, typically during the acute care, whilst the follow-up neuropsychological data and vocational data were gathered and complemented during follow-up visits. The follow-up visits took place three months, six months, one year (partial sample only) and two years after the stroke. In this subset of studies, baseline, six-month and two-year follow-up data was utilized. Complementary registry data on patients’ income supplements were retrieved from the Finnish Social Insurance Institution (Kela) and the Finnish Centre for Pensions (ETK) databases. The Ethics Committee of Helsinki University Central Hospital approved the study and the consent procedure, and all participants provided signed informed consent for clinical data acquisition. Informed consents for registry data acquisition were requested separately, and registry data were retrieved only for patients who provided separate signed informed consent for registry data acquisition.
3.3 Participants

The participants were enrolled from a consecutive sample of all eligible patients who were admitted to the clinics. The inclusion criteria were a first-ever diagnosed supratentorial ischaemic stroke in native Finnish-speaking patients between the ages of 18 and 65 years. Based on clinical history and patient reports, patients were excluded if they had neurological or psychiatric history or comorbidity potentially promoting cognitive impairments.

A control group, which consisted of 50 healthy subjects with similar demographic characteristics who were eligible based on all of the inclusion/exclusion criteria except for the stroke, was also assessed according to an identical written study protocol as the patients. The controls were recruited from the spouses, siblings and friends of the patients. The controls were assessed twice, with a three-month interval between the assessments.

3.4 Demographic and clinical measures

The sexes and ages (years) of the study participants were compiled from the participants' medical records. The educational status (years of education) was obtained from clinical interviews.

The data on major vascular risk factors included atrial fibrillation, diabetes, hypercholesterolaemia, hypertension, overweight (Body Mass Index > 25) and smoking, and were collected from the medical records and clinical interviews at the time of the baseline neuropsychological assessment. The accumulation sum score of the vascular risk factors (0-6) was used in the analyses.

An experienced stroke neurologist visually evaluated lesion location and size of the infarction were from computerized tomography (CT) or magnetic resonance imaging (MRI) routinely obtained in the course of standard clinical care. The locations were categorised as frontal, parietal, temporal, occipital, basal ganglia, multiple with more than one location, or non-visible. The infarct size was categorised using a modified version of Paciaroni et al. (2008) as small (< 1.5 cm), medium (1.5 - 4.0 cm) or large (> 4.0 cm). Incident silent infarcts
and leukoaraiosis were binary encoded. The pathophysiological aetiologies of the infarcts were categorised according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification scheme (Adams et al., 1993).

NIHSS (Brott et al., 1989) and Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) total sum scores were recorded upon hospital admission and upon discharge from the acute care unit. In addition, the functional independence was evaluated using the Barthel Index (Mahoney & Barthel, 1965) upon the baseline neuropsychological assessment.

### 3.5 Cognitive data

Cognitive data from both the patients and the control subjects were gathered at the hospital facilities using neuropsychological assessments administered by clinical neuropsychologists following a written study protocol. Baseline neuropsychological assessments of the patients were completed within the first weeks of their strokes, after the treating neurologist had determined that each patient was ready to be discharged from the acute care unit. The timing of the baseline assessments was chosen to minimize bias in the neuropsychological data caused by fluctuating acute conditions such as delirium or fatigue.

Neuropsychological assessments included measures of seven cognitive domains: executive functions, psychomotor speed, episodic memory, working memory, language, visual spatial and constructional skills, and motor skills. Each cognitive domain was measured with three separate tests as follows. **Executive functions** were measured with the time to complete Trail Making Test Part B (Poutiainen, Kalska, Laasonen, Närhi, & Räsänen, 2010; Reitan, 1958), the number of words within one minute in the phonemic fluency task (Lezak, Howieson, Bigler, & Tranel, 2012) and the number of correct responses in the Go/no-go task (Dubois, Slachevsky, Litvan, & Pillon, 2000). **Psychomotor speed** was measured with the time to complete the Trail Making Test Part A (Poutiainen et al., 2010; Reitan, 1958), time per correct response in the copying tasks (Carlesimo, Fadda, & Caltagirone, 1993; Lezak et al., 2012) and time per correct response in the modified 12-item Token Test (De Renzi & Faglioni, 1978) with the large tokens only. **Episodic memory** was measured with a sum score of
immediate and delayed recall in the Wechsler Memory Scale Revised Logical Memory I and II (Wechsler, 1987), the sum of correct responses in learning a series of 10 unrelated words (Christensen, 1979) with an added delayed recall score and sum score of a shortened and modified Benton Visual Retention Test (Benton, 1974) (five odd numbered figures of Part C) with added delayed recall and delayed recognition scores. Working memory was measured with the Digit Span subtest of the Wechsler Adult Intelligence Scale, Third Edition (Wechsler, 1997), the number of correct responses in the homogeneous interference task (Christensen, 1979) and the number of correct responses in the heterogeneous interference task (Christensen, 1979). Language was measured with the sum of correct responses in the modified 12-item Token Test (De Renzi & Faglioni, 1978) with the large tokens only, a shortened 31-item Visual Naming task score from the Assessment of Aphasia and Related Disorders (the early version of the Boston Diagnostic Aphasia Examination) (Laine, Niemi, Koivuselkä-Sallinen, & Tuomainen, 1997) and the number of correctly repeated words in the repetition of a long sentence with 11 words (Christensen, 1979). Visual spatial and construction skills were measured with the number of correct figures in copying of 4 geometric figures (Lezak et al., 2012) scored according to Carlesimo et al. (1993), the number of correct responses in drawing clock arms into 10 empty clock frames according to a digit model (Adunsky, Fleissig, Levenkrohn, Arad, & Noy, 2002; Lezak et al., 2012) and the visuospatial searching task (Vilkki, 1989). The visuospatial searching task is a variant from commonly used paper and pencil tests used to detect hemispatial neglect. In the task, the subject has a paper sheet full of drawn straight lines with different orientations, and a marked reference line in the middle of the paper. The subject is instructed to mark all the lines that have specifically the same orientation with the reference line as quickly and errorless as possible. After a practice phase, the task is repeated four times each with differing line orientations. Here, the task was scored as the sum of correct responses across the four sheets. Motor skills were measured with the bimanual hand movements task (Christensen, 1979), the fist-palm-edge task (Christensen, 1979) and finger tapping test (Lezak et al., 2012). In the finger tapping test, the subject is instructed to tap a tapping device with the index finger as many times as possible within a ten second frame. The task is
first practiced and then repeated four times alternating left and right hands and scored as a sum of averaged left and right hand tapping results.

Internal consistency (Cronbach $\alpha$) of the cognitive domains calculated among the total patient group ranged from $\alpha = .72$ (psychomotor speed) to $\alpha = .91$ (language).

Post-stroke cognitive impairments were defined mimicking clinical decision-making, where a repeated pattern of errors is valued clinically relevant. This requirement for multiple within-domain failures when defining cognitive impairments was used to enhance the specificity of the cognitive impairments across a range of situational factors. Specifically, a single test score was considered deficient if a patient scored below the 10th percentile for that test compared with the performance of the control group. If at least two test scores within the same cognitive domain were deficient, a cognitive impairment was assumed to exist.

To describe a global, cross-domain severity of cognitive impairments, the number of cognitive impairments for each patient was counted. To avoid bias due to learning, patient follow-up data were compared with control follow-up data.

**3.6 Mood state, apathy and fatigue**

Mood state was evaluated as part of neuropsychological assessments with a modified Profile of Mood States (POMS; McNair & Lorr, 1964) questionnaire covering questions on mood, apathy and fatigue at the baseline evaluation with a 10-item version, and at follow-ups with a 38-item version. Total symptom sum scores were used in the analyses to control for the effect of altered mood state, apathy and fatigue to the cognitive performance. In the analyses, the 90th percentile level of the control group’s symptom sum score was used as the cut-off for an impaired mood state.
3.7 Vocational data

The vocational status and type of work were collected in a clinical interview as a part of the baseline neuropsychological assessment. At follow-up visits, the patients’ vocational statuses were recollected with a questionnaire modified from that of Sheehan et al. (1996).

Post hoc, the vocational statuses were crosschecked against the registry data, as described in detail in the next section (3.8) on income supplement use. The inability to return to work was defined as not returning to paid employment outside the house, either full- or part-time. If a patient was on sick leave or disability pension at the six-month follow-up, the diagnoses in the related medical certificate were verified to assure the sick leave or pension in question actually was caused by the stroke and not any other disease or medical condition.

The type of work was classified as managerial employee, clerical employee, employee, entrepreneur or student. A managerial employee refers to occupations typically requiring an academic degree, often but not always a managerial position with several subordinates, for instance, medical doctors and chief executive officers. A clerical employee designates occupations that require a vocational degree below the academic degree, including many types of office jobs, such as secretary and bookkeeper. An employee indicated manual labour, for example, construction worker and housekeeper. An entrepreneur designates practitioners, freelancers, professional workers and self-employed persons. A student refers to full-time students.

3.8 Income supplements use

Income supplement use data were primarily based on registry data acquired from the Finnish Social Insurance Institution (Kela) and the Finnish Centre for Pensions (ETK). Additional data were collected using a questionnaire modified from that of Sheehan et al. (1996), which was completed by the patients during their neuropsychological assessments.
The registry data covered time from the dates of the patients’ strokes till three years after the strokes. The registry data included timely information about following income supplements provided in Finland at the time of the study: sickness allowances, rehabilitation allowances, disability pensions, earning-related pensions, national pensions, guarantee pensions, disability allowances, care allowances for pensioners, basic unemployment allowances, and labour market subsidies.

The registry data did not include information on earnings-related unemployment allowances, study grants, general housing allowances, housing allowances for pensioners, housing supplements for students, housing assistance for conscripts, pensions paid from abroad; for this information, questionnaire data was applied (excluding all housing benefits). Any score above zero in the stroke-related allowance-use variable refers to the time (in months) during which a patient received one or more benefits granted specifically on the basis of the stroke diagnosis (possible alternatives are sickness allowance, rehabilitation allowance, disability pension, disability allowance, or care allowance) within the three-year period after the stroke.

The aim was to measure the specific impact of stroke on the use of income supplements and to avoid any bias introduced by payments for other reasons. Therefore, when calculating the stroke-related time of income supplement use, any payments that a patient had been receiving before the stroke were removed from consideration. For example, if a patient was receiving an age-related pension or disability benefits at the time of stroke and continued to receive the same benefits after the stroke, then the patient’s stroke-related income supplement use was encoded as zero. If a patient was receiving stroke-related disability benefits after the stroke but reached retirement pension age during the three-year follow-up period, then only the stroke-related income supplements received before the age-related pension benefits began were encoded as stroke-related income supplement use.
3.9 Statistical analyses

The statistical analyses were computed with the IBM SPSS Statistics Version 20.0, 21.0 or 22.0 (International Business Machines Corporation, Armonk, New York, USA).

All neuropsychological tests were administered to all participants, and test failures (e.g., due to severe aphasia or neglect) were scored as zero points or the maximum time. A total of ten cells with missing data in the data matrix, found within six different neuropsychological test scores of the patients, were imputed using the patient group means of the variables. Profile of Mood States data was missing on 11 patients. Whenever possible, missing registry-based income supplement data were crosschecked with the patients’ questionnaire data and then imputed accordingly.

Univariate comparisons between the patients and controls, the dropout analysis, and associations between independent and dependent variables were calculated using *t*-tests, *U*-tests, χ²-statistics, Pearson or Spearman correlations, or one-way ANOVA depending on variable distributions. In Spearman correlations used in Study I, cognitive impairments refer to the numbers of defective within-domain test performances (0–3) for each of the seven cognitive domains.

Multivariate analyses were performed with logistic regression models (Study I and II) and survival (Cox) models (Study III). In the comparison of clinical and cognitive severity of stroke (Study I), enter-method binary logistic regression models adjusted for gender, age and education (years) were calculated for those cognitive domains that had a significant correlation with NIHSS scores. In addition, the total number of cognitive impairments (zero, one, two or at least three) and the presence of at least one cognitive impairment were also calculated to characterize global, cross-domain cognitive dysfunction.

When assessing the role cognitive impairments in stroke patients’ inability to return to work (Study II), those predictors with a significant univariate association with return-to-work were chosen for the enter-method binary
logistic regression model comparing the significant predictors of the inability to return to work.

In the analysis of stroke-related income-supplement use (Study III), the predictors that had significant univariate associations with the use of stroke-related income supplements were selected as the covariates for subsequent multivariate survival (Cox) models using the enter method. The duration of the use of stroke-related income supplements, in months, was set as the time variable. Three separate models were built, each using one of the neuropsychological data sets (collected at baseline, six months, and two years after the stroke).
4 Results

4.1 Sample characteristics

Figure 1 presents the sample acquisition as a flow diagram. During data collection, 38 patients refused to participate, 19 were lost due to logistic reasons such as quick discharges or hospital transfers, and 6 severely injured patients were excluded because they could not complete the neuropsychological assessments. A total of 230 patients initially participated in the study, of which 186 (80.9%) were treated and assessed in Helsinki University Central Hospital, and 44 (19.1%) in Lapland Central Hospital. All together, 15 neuropsychologists participated in the data collection procedure. Among the total patient group, 197 patients remained in the study at the six-month follow-up, and 166 patients remained at the two-year follow-up. The 33 patients who were lost to the six-month follow-up were less educated (mean $[M] = 11.1$ years, standard deviation $[SD] = 2.80$ versus $M = 12.1$, $SD = 2.67$, $t_{228} = 22.02$, $p = .045$) and more likely to have leukoaraiosis than were the patients who continued to participate in the study (39.4% of the patients lost to follow-up versus 22.4% of the ongoing study participants; $\chi^2_{1} = 4.34$, $p = .037$). The patients who were lost at the six-month follow-up also had a higher mean rank NIHSS score at the time of hospital admission (median = 3, range = 0–24 versus median = 3, range = 0–17, $U = 2505.5$, $p = .033$) and a higher number of baseline cognitive impairments than those of the patients who participated in the six-month follow-up (median = 2, range = 0–7 versus median = 1, range = 0–7, $U = 2488.5$, $p = .022$). Comparing the participants in the two-year follow-up with those 31 lost to follow-up, more frequent cognitive impairments were observed in the dropout group than in the participants (median = 3, range = 0–7 versus median = 1, range = 0–7, $U = 1526.5$, $p = .004$). No significant differences were found with regard to other characteristics, i.e. sex, age, vascular risk factors, aetiology (TOAST), lesion size, silent infarcts, NIHSS scores at discharge, functional independence (Barthel Index), or mood state, apathy and fatigue (POMS), between the patients lost to follow-up and those who participated in the study at each follow-up examinations.
The initial cohort with 230 patients included 146 men (63.5 %), had a mean age of 54.0 years ($SD = 9.82$), a mean of 12.0 years of education ($SD = 2.71$) and a median of three (range = 0–6) vascular risk factors. The controls were demographically similar to the patient group, but they had fewer vascular risk factors (median = 2, range = 0–5, $U = 4434.0, p = .009$) and reported fewer mood state, apathy and fatigue symptoms (POMS median 11.0, range = 0–32 versus median = 7.5, range = 0–21, $U = 2696.0, p < .001$). The participants are characterized in detail in Table 1. In study III, the full data from 230 patients was examined.

In study I, 223 patients were analysed. The clinical interview of the patients covered developmental learning disabilities. Seven patients reported in the
interview that as a child they had had a learning disability. In study I, the specificity of the reported post-stroke cognitive impairments was evaluated to be so important to the credibility of the results that it was decided these seven patients would be excluded based on their subjective reports of learning disability. Eventually, excluding these patients remained more theoretically than empirically motivated, as these seven patients did not significantly differ from others with regard to sex, age, education, number of vascular risk factors, aetiology, lesion size, NIHSS or GCS at either measurements, or number of cognitive deficits at any of the assessments.

Regarding characteristics of Study II, the criterion of working outside the house prior to the stroke was fulfilled in 161 of the 230 patients, and of those, 140 patients (60.9 % of the 230 patients) completed the follow-up assessment and were thus analysed.

4.2 Clinical characteristics

The average ($M$) duration of hospital stays in the full cohort of 230 patients was 9.04 days ($SD = 5.12$). At hospital admission, patients scored a median of three (range = 0–24) in NIHSS and 90.0 % ($N = 207$) of the patients had gross neurological findings with a NIHSS score above zero. At the discharge from the acute care unit, 68.7 % ($N = 158$) patients still had a NIHSS score of one or more (median = 1, range = 0–16). GCS median was 15 both at hospital admission (range = 10–15) and at discharge from the acute care unit (range = 2–15). The cohort also recovered well functionally as the Barthel Index median was 100 (range = 25–100) at the time of the baseline neuropsychological assessment.

Large-artery atherosclerosis was the dominant pathophysiological aetiology ($N = 58$, 25.2 %) of the strokes. Small-artery occlusion accounted for 23.5 % of the strokes ($N = 54$) and cardioembolism 21.3 % ($N = 49$), respectively. Hypertension ($N = 87$, 62.1%) and hypercholesterolaemia ($N = 79$, 56.4%) were the most frequent vascular risk factors of the patients.

Typical brain lesions of the patients were small (< 1.5 cm, $N = 97$, 42.2 %) or intermediate (1.5-4.0 cm, $N = 55$, 23.9 %) in size while 13.9 % of the patients ($N = 32$) had a stroke with the largest diameter of over 4.0 cm. In 20.0 % of the
patients ($N = 46$) the diagnoses of ischaemic stroke were based on clinical features without visible brain imaging findings. Imaging revealed a silent infarct in 24.3 % ($N = 56$) and leukoaraiosis in 24.8 % ($N = 57$) of the patients.

By the end of the two-year follow-up period, recurrent stroke was identified in 7.0 % ($N = 16$) of the patients and 2.6 % ($N = 6$) had deceased.
### Table 1. Characteristics of 230 stroke patients and 50 control participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (N)</td>
<td>146 (63.5 %)</td>
<td>31 (62.0 %)</td>
<td>.844</td>
</tr>
<tr>
<td>Age (mean [M])</td>
<td>54.0 (SD = 9.8)</td>
<td>54.3 (SD = 9.0)</td>
<td>.850</td>
</tr>
<tr>
<td>Education (M)</td>
<td>12.0 (SD = 2.7)</td>
<td>12.4 (SD = 2.9)</td>
<td>.396</td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (N)</td>
<td>25 (10.9)</td>
<td>1 (2.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Type I (N)</td>
<td>5 (2.3 %)</td>
<td>0 (0.0 %)</td>
<td>n/a</td>
</tr>
<tr>
<td>Type II (N)</td>
<td>25 (10.9 %)</td>
<td>3 (6.0 %)</td>
<td>n/a</td>
</tr>
<tr>
<td>Hypercholesterolemia (N)</td>
<td>139 (60.4 %)</td>
<td>29 (58.0 %)</td>
<td>.750</td>
</tr>
<tr>
<td>Hypertension (N)</td>
<td>154 (67.0 %)</td>
<td>29 (58.0 %)</td>
<td>.228</td>
</tr>
<tr>
<td>Overweight (N)</td>
<td>154 (67.0 %)</td>
<td>35 (70 %)</td>
<td>.677</td>
</tr>
<tr>
<td>Smoking (N)</td>
<td>88 (38.3 %)</td>
<td>9 (18.0 %)</td>
<td>.006</td>
</tr>
<tr>
<td>Number of vascular risk factors (N)</td>
<td>3 (range = 0–6)</td>
<td>2 (range = 0–5)</td>
<td>.009</td>
</tr>
<tr>
<td><strong>Aetiology (TOASTa)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis (N)</td>
<td>58 (25.2 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolism (N)</td>
<td>49 (21.3 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small-artery occlusion (N)</td>
<td>54 (23.5 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, determined (N)</td>
<td>21 (9.1 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetermined (N)</td>
<td>48 (20.9 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lesion size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1.5 cm (N)</td>
<td>97 (42.2 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5-4.0 cm (N)</td>
<td>55 (23.9 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 4.0 cm (N)</td>
<td>32 (13.9 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion not visible (N)</td>
<td>46 (20.0 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent infarct (N)</td>
<td>56 (24.3 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukoaraiosis (N)</td>
<td>57 (24.8 %)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Stroke severity (NIHSSc)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission (median)</td>
<td>3 (range = 0–24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge (median)</td>
<td>1 (range = 0–16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional independence (Barthel Index median)</td>
<td>100 (range = 25–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mood state, apathy and fatigue (POMS)d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (N = 217, median)</td>
<td>12 (range = 1–32)</td>
<td>7.5 (range = 0–21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Six-month follow-up (N = 187, median)</td>
<td>35 (range = 0–149)</td>
<td>25.5 (range = 0–89)</td>
<td>.032</td>
</tr>
<tr>
<td>Two-year follow-up (N = 161, median)</td>
<td>35 (range = 2–136)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aTrial of ORG 10172 in Acute Stroke Treatment classification scheme; bLesion size was visually evaluated from computerized tomography (CT) or magnetic resonance imaging (MRI) routinely obtained in the course of standard clinical care. The infarct size was categorised using a modified version of Paciaroni et al. (2008); cNational Institutes of Health Stroke Scale; dProfile of Mood States questionnaire, at baseline a shortened 10-item version, at follow-ups the full 30-item version was used; eControls were re-examined after three months.
4.3 Cognitive impairments, mood state, apathy and fatigue

The baseline, six-month follow-up and two-year follow-up neuropsychological assessments were conducted an average of eight days (SD = 4.36), 186 days (SD = 14.01), and 745 days (SD = 58.96) after the strokes, respectively. The duration of the assessments was approximately 1.5-2.5 hours depending on the condition and functioning of the patients. At the baseline assessment, 56.5 % of the patients (130/230 patients) exhibited cognitive impairments. At six months, the proportion of patients with cognitive impairments had significantly fallen to 46.7 % (92/197 patients, $\chi^2_1 = 51.49, p < .001$). At the two-year follow-up, the proportion of patients with cognitive impairments was further reduced to 44.0 % (73/166 patients), but this reduction was not statistically significant ($\chi^2_1 = .50, p = .482$). Psychomotor slowness and executive dysfunction were the most prevalent cognitive impairments throughout the two-year follow-up period. Figure 2 presents the prevalences of cognitive impairments from the baseline through the follow-up. Mood state, apathy and fatigue data were available for 217 patients at baseline, 187 patients at the six-month follow-up and 161 patients at the two-year follow-up. As a group, the patients expectedly reported more mood state, apathy and fatigue symptoms than the controls (baseline: median = 12.0, range = 1–32 versus median = 7.5, range = 0–21, $U = 2969.0, p < .001$; follow-up [patients: six-month; controls: three-month]: median = 35.0, range = 0–149 versus median = 25.5, range = 0–89, $U = 3423.0, p = .032$).
Figure 2. The prevalence of cognitive impairments at the baseline assessment completed within the first weeks after stroke (N = 230), at six-month follow-up (N = 197) and at two-year follow-up (N = 166). Each cognitive domain was measured with three separate tests. A single test score was considered deficient if a patient scored below the 10th percentile compared with the performance of the control group. If at least two test scores within the same cognitive domain were deficient, a cognitive impairment was assumed to exist.

4.4 Vocational characteristics

Vocational characteristics refer here to Study II with a subset of 140 patients both working full-time outside the house before the stroke and participating in the six-month follow-up. Of those, employees were the biggest occupational subgroup (N = 61, 43.6 %) followed by managerial employees (N = 37, 26.4 %), clerical employees (N = 26, 18.6 %), entrepreneurs (N = 11, 7.9 %) and students (N = 5, 3.6 %). By six months after the stroke, 41.4 % of the patients (N = 58)
had succeeded in returning to work. Regarding the remaining 58.6 % of the patients (\(N = 82\)), 46.4 % (\(N = 65\)) were still on sick leave, and 2.9 % (\(N = 4\)) were on a disability pension, 5.0 % (\(N = 7\)) were unemployed and 4.3 % (\(N = 6\)) of the patients had retired. Figure 3 presents the vocational characteristics of these 140 patients who were employed and working at the time of their stroke, stratified by the type of work.
Figure 3. The six-month vocational outcome stratified by the type of work in 140 stroke patients who were employed at the time of first-ever ischaemic stroke.
4.5 Stroke-related income supplements use

A total of 175 patients granted permission for registry searches of their income supplement use. The patients with available registry data had higher levels of education ($M = 12.2, SD = 2.66$ versus $M = 11.2, SD = 2.72$, $t_{228} = -2.47, p = .014$), lower NIHSS scores at hospital admission (median = 2, range = 0–20 versus median = 4, range = 0–24, $U = 3671.0, p = .007$) and longer duration of stroke-related income supplements use ($M = 8.0, SD = 12.7$ versus $M = 12.6, SD = 15.3$, $t_{107.9} = -2.24, p = .027$) than those of the patients without registry data. Complementary questionnaire data on income supplements were initially available for 229 patients; these data were available for 207 patients at the six-month follow-up and 174 patients at the two-year follow-up. By combining the registry data with the questionnaire data and assuming that permanent income supplements would continue for up to three years among the 55 patients with missing registry data, the stroke-related income supplements could be calculated over three years after stroke for all 230 patients.

At the time of the stroke, 72.2 % of the patients ($N = 166/230$ patients) were not receiving any income supplements, whereas three years later, only 29.6 % ($N = 68/230$ patients) were not receiving any form of income supplement. Stroke specifically caused a mean of 11.5 months ($SD = 14.82$, range = 0–36) of additional income supplement use among the patients, while 69.1 % of the patients ($N = 159/230$ patients) received income supplements due to their strokes. These payments continued until three months in 54.8 % ($N = 126 / 230$ patients) and up to six months in 39.1 % of the patients ($N = 90/230$ patients). One year after the stroke 31.3 % of the patients ($N = 72/230$ patients), at two years 25.7 % ($N = 59/230$ patients), and at three years 23.5 % ($N = 54/230$ patients), still received stroke-related income supplements. Figure 4 presents the use of income supplements in the cohort at baseline and at the three-year follow-up.
Figure 4. The use of income supplements in 230 stroke patients at the time of a first-ever ischaemic stroke and at the three-year follow-up.

4.6 Comparison of clinical and cognitive severity of stroke

All the correlations between the NIHSS admittance scores and impairments in all seven cognitive domains reached statistical significance ($p < .01$) and ranged from $r = .18$ (episodic memory) to $r = .40$ (motor skills). The NIHSS discharge score correlations with cognitive impairments equally reached significance ($p < .01$) for all seven cognitive domains but the correlations were systematically stronger, with correlations ranging from $r = .34$ (working memory) to $r = .44$ (motor skills).

Separate logistic regression models adjusted for gender, age and education were computed to predict domain-specific cognitive impairments within the first weeks after the stroke with NIHSS scores upon admittance and discharge. Adjusted for demographics, the NIHSS discharge score stably predicted cognitive impairments with odds ratios ($OR$) ranging from $OR = 1.37$ (95% CI =
1.18–1.60) for episodic memory to $OR = 1.87$ (95% CI = 1.52–2.29) for motor skills. The NIHSS score at discharge was systematically more effective in predicting impairments than the admittance score. The predictive models had rather high specificities, which ranged from 89.5–97.7 %, but the sensitivities were as low as 11.6–47.9 %. Approximately two patients out of five with a NIHSS score of zero (41.0 %) had baseline cognitive impairments, as did over half of the patients (54.0 %) with a score of one. Among patients with NIHSS scores of two or three the prevalence of baseline cognitive impairments increased linearly, and all patients in this functionally well-recovered working-age cohort who had NIHSS scores of four or higher exhibited cognitive impairments. The prevalence of all seven domain-specific cognitive impairments except for the motor skills lowered significantly ($p < .05$) from the baseline to the follow-up, yet the common relationship between cognitive impairments and even the lowest NIHSS scores persisted at the six-month follow-up. Figure 5 presents the accumulation of cognitive impairments stratified to the NIHSS scores.
To control for confounding factors, those patients with cognitive impairments ($N = 136 / 223$) were compared to cognitively intact patients ($N = 87 / 223$). The occurrence of cognitive impairments was not accountable for the accumulation of six principal vascular risk factors (median = 3, range = 0–6 versus median = 3, range = 0–5, $U = 4919.5$, $p = .071$), silent infarcts (27.2 % [$N = 37$] versus 20.7 % [$N = 18$], $\chi^2 = 1.11$, $p = .291$), leukoaraiosis (27.2 % [$N = 37$] versus 23.0 % [$N = 20$], $\chi^2 = .73$, $p = .393$), nor mood state (median = 13, range = 1–31 versus median = 11, range = 2–32, $U = 4547.5$, $p = .052$). To further test the role of these possibly confounding factors the comparisons were rerun for those 135 patients with the lowest NIHSS scores of 0-1 at discharge from the acute care unit. This repeat analysis did not alter the results as none of the factors saturated significantly in the subgroups of 64 cognitively impaired and 71 intact
patients (vascular risk factors: median = 3, range = 0–6 versus median = 3, range = 0–5, \( U = 1871.0, p = .123 \); silent infarcts: 31.3 % [\( N = 20 \)] versus 22.5 % [\( N = 16 \)], \( \chi^2 = 1.67, p = .196 \); leukoaraiosis: 32.8 % [\( N = 21 \)] versus 23.9 % [\( N = 17 \)], \( \chi^2 = 1.20, p = .274 \); mood state, apathy and fatigue: median = 13, range = 1–31 versus median = 11, range = 2–32, \( U = 1863.0, p = .156 \)).

4.7 Model of return to work after stroke

The model predicting return to work after stroke was built on the basis of significant one-way associations between predictors and return-to-work outcome. Age (\( t_{138} = -3.25, p = .001 \)) and education (\( t_{138} = 2.15, p = .033 \)), but not sex (\( \chi^2 = .23, p = .628 \)), were related to the inability to return to work. The type of work did not quite reach significance (\( \chi^2 = 8.674, p = .070 \)), but as an exception was nevertheless included in the final model because of the variable’s general relevance to the study.

The NIHSS (admittance: \( U = 1475.0, p < .001 \); discharge: \( U = 1155.5, p < .001 \)) and GCS scores (admittance: \( U = 1874.0, p = .003 \); discharge: \( U = 2088.0, p = .006 \)) and TOAST (\( \chi^2 = 12.20, p = .016 \)) were associated with the inability to return to work and included in the final model. In total, 72.2 % (\( N = 26 / 36 \)) of the patients in the large artery atherosclerosis group, 71.0 % (\( N = 22 / 31 \)) in the cardioembolism group and 66.7 % (\( N = 10 / 15 \)) in the other determined cause group were unable to return to work. Regarding patients with small-artery occlusion or undetermined cause, 41.4 % (\( N = 12 / 29 \)) did not return to work. The size of the lesion (\( U = 11.7, p = .008 \)) as the only significant radiological factor and Barthel Index (\( U = 1607.0, p < .001 \)) also had a significant one-way association with the outcome and were included in the final model.

All baseline impairments across seven cognitive domains significantly associated with the outcome (\( p < .001 \) except for working memory \( p = .002 \)). At the six-month follow-up, all but the visual spatial and constructional skills (\( p = .413 \)) had a significant (\( p < .01 \)) one-way association with the inability to return to work (except for motor skills \( p = .016 \)). In contrast, mood state, apathy and
fatigue (POMS) were not associated with the outcome neither at baseline ($\chi^2 = 1.40, p = .237$) nor at the six-month follow-up ($\chi^2 = 1.68, p = .195$).

In order to eliminate excess multicollinearity in the final model, the predictor variable list was modified as follows. For the NIHSS and GCS, only the measurement with a stronger univariate association (NIHSS: discharge, GCS: admittance) was selected for the final model. The baseline cognitive data were included in the model as the number of cognitive impairments. The cognitive follow-up data were included in the model as the persistence of cognitive impairments.

The final model is presented in Table 2. In the model, only the number of baseline cognitive impairments ($OR = 2.25, 95\% CI = 1.29–3.92, p = .004$) was a significant predictor. Compared with a patient with no baseline cognitive impairments, each cognitive impairment a patient had more than doubled the risk of the inability to return to work. The persistence of baseline cognitive impairments was the only other predictor that came close to reaching the level of significance ($OR = 2.72, 95\% CI = .94–7.86, p = .064$).
Table 2. Logistic regression model of the inability to return to work six months after a first-ever ischaemic stroke.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Wald (df)</th>
<th>p</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Number of cognitive impairments(a)</td>
<td>8.24 (1)</td>
<td>.004</td>
<td>2.25</td>
<td>1.29</td>
</tr>
<tr>
<td>Persistence of impairments(b)</td>
<td>3.42 (1)</td>
<td>.064</td>
<td>2.72</td>
<td>.94</td>
</tr>
<tr>
<td>Age</td>
<td>1.20 (1)</td>
<td>.274</td>
<td>1.04</td>
<td>.97</td>
</tr>
<tr>
<td>Education years</td>
<td>.00 (1)</td>
<td>.993</td>
<td>1.00</td>
<td>.79</td>
</tr>
<tr>
<td>Type of work(c)</td>
<td>1.14 (4)</td>
<td>.888</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clerical employee</td>
<td>.44 (1)</td>
<td>.507</td>
<td>.57</td>
<td>.11</td>
</tr>
<tr>
<td>Employee</td>
<td>.03 (1)</td>
<td>.871</td>
<td>.89</td>
<td>.20</td>
</tr>
<tr>
<td>Entrepreneur</td>
<td>.50 (1)</td>
<td>.481</td>
<td>.48</td>
<td>.06</td>
</tr>
<tr>
<td>Student</td>
<td>.30 (1)</td>
<td>.582</td>
<td>.40</td>
<td>.02</td>
</tr>
<tr>
<td>Stroke severity (NIHSS)(d)</td>
<td>2.56 (1)</td>
<td>.110</td>
<td>1.53</td>
<td>.91</td>
</tr>
<tr>
<td>Stroke severity (GCS)(e)</td>
<td>1.41 (1)</td>
<td>.235</td>
<td>.75</td>
<td>.47</td>
</tr>
<tr>
<td>Aetiology (TOAST(f))</td>
<td>3.12 (4)</td>
<td>.537</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>.18 (1)</td>
<td>.676</td>
<td>.74</td>
<td>.18</td>
</tr>
<tr>
<td>Small-artery occlusion</td>
<td>1.79 (1)</td>
<td>.181</td>
<td>.38</td>
<td>.09</td>
</tr>
<tr>
<td>Other determined</td>
<td>.15 (1)</td>
<td>.701</td>
<td>1.49</td>
<td>.20</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1.05 (1)</td>
<td>.305</td>
<td>.47</td>
<td>.11</td>
</tr>
<tr>
<td>Lesion size</td>
<td>.01 (1)</td>
<td>.943</td>
<td>.98</td>
<td>.55</td>
</tr>
<tr>
<td>Functional independence (Barthel Index)(a)</td>
<td>2.12 (1)</td>
<td>.145</td>
<td>.92</td>
<td>.83</td>
</tr>
<tr>
<td>Constant</td>
<td>1.99 (1)</td>
<td>.158</td>
<td>11747.11</td>
<td></td>
</tr>
</tbody>
</table>

\(a\)Baseline; \(b\)Persistence = compared with baseline, no improvement at six-month follow-up; \(c\)Managerial employee = occupations typically requiring an academic degree, clerical employee = occupations requiring a vocational degree below the academic degree, employee = manual labour, entrepreneur = e.g. practitioners and self-employed persons, student = full-time students; \(d\)National Institutes of Health Stroke Scale, measured at discharge from the acute care unit; \(e\)Glasgow Coma Scale, measured at admittance to hospital; \(f\)Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification scheme; The inability to return to work is the predicted category; The reference category for the type of work is managerial employee; The reference category for aetiology is large-artery atherosclerosis.
4.8 Models of stroke-related income supplements use

The predictors of stroke-related income supplements use were chosen for the multivariate models based on significant univariate associations, described in detail in Table 3. The presence of atrial fibrillation, use of an income supplement before experiencing a stroke, NIHSS score at hospital discharge, Barthel Index score, lesion size, and mood state, apathy and fatigue at the six-month and two-year follow-ups, as well as most of the cognitive variables at each assessment, were significantly associated with the use of income supplements and were thus included in the subsequent multivariate survival models. Similarly as when predicting return to work, the number of cognitive impairments was chosen to collectively represent the cognitive function data in the models to avoid excessive multicollinearity among the predictor variables.
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Test value</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>( t_{228} = .55 )</td>
<td>.586</td>
</tr>
<tr>
<td>Age</td>
<td>( r_{Pearson} = .00 )</td>
<td>.948</td>
</tr>
<tr>
<td>Education</td>
<td>( r_{Pearson} = .01 )</td>
<td>.883</td>
</tr>
<tr>
<td>Accumulated vascular risk factors</td>
<td>( r_{Spearman} = .06 )</td>
<td>.372</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>( t_{43.2} = -2.41 )</td>
<td>.020</td>
</tr>
<tr>
<td>Diabetes</td>
<td>( t_{228} = -.90 )</td>
<td>.370</td>
</tr>
<tr>
<td>Hypertension</td>
<td>( t_{160.7} = -1.41 )</td>
<td>.162</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>( t_{179.3} = 1.39 )</td>
<td>.166</td>
</tr>
<tr>
<td>Overweight</td>
<td>( t_{228} = -1.21 )</td>
<td>.229</td>
</tr>
<tr>
<td>Smoking</td>
<td>( t_{228} = .91 )</td>
<td>.366</td>
</tr>
<tr>
<td>Income supplement use before stroke</td>
<td>( t_{177.4} = 6.69 )</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Stroke severity (NIHSS(^a))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission</td>
<td>( r_{Spearman} = .12 )</td>
<td>.070</td>
</tr>
<tr>
<td>Discharge</td>
<td>( r_{Spearman} = .28 )</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Functional independence (Barthel Index)</td>
<td>( r_{Spearman} = -0.24 )</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Aetiology (TOAST(^b))</td>
<td>( F_4 = 1.91 )</td>
<td>.109</td>
</tr>
<tr>
<td>Lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>( r_{Spearman} = .25 )</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Location</td>
<td>( F_8 = 1.87 )</td>
<td>.066</td>
</tr>
<tr>
<td>Vascular degeneration</td>
<td>( t_{228} = .31 )</td>
<td>.755</td>
</tr>
<tr>
<td>Silent infarcts</td>
<td>( t_{228} = .43 )</td>
<td>.665</td>
</tr>
<tr>
<td>Cognitive impairments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive function</td>
<td>( t_{122.7} = -3.25 )</td>
<td>.001</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>( t_{151.7} = -3.32 )</td>
<td>.001</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>( t_{63.4} = -3.57 )</td>
<td>.001</td>
</tr>
<tr>
<td>Working memory</td>
<td>( t_{228} = -1.79 )</td>
<td>.074</td>
</tr>
<tr>
<td>Language</td>
<td>( f_{48.4} = -3.02 )</td>
<td>.004</td>
</tr>
<tr>
<td>Visuospatial and construction skills</td>
<td>( t_{103.0} = -3.20 )</td>
<td>.002</td>
</tr>
<tr>
<td>Motor skills</td>
<td>( f_{83.1} = -3.55 )</td>
<td>.001</td>
</tr>
<tr>
<td>Number of cognitive impairments</td>
<td>( r_{Spearman} = .26 )</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Six-month follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive function</td>
<td>( t_{70.9} = -1.32 )</td>
<td>.192</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>( t_{11.6} = -3.37 )</td>
<td>.001</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>( t_{99.3} = -2.45 )</td>
<td>.019</td>
</tr>
<tr>
<td>Working memory</td>
<td>( t_{195.3} = -3.56 )</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Language</td>
<td>( t_{195} = -3.75 )</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Visuospatial and construction skills</td>
<td>( t_{52.3} = -1.49 )</td>
<td>.149</td>
</tr>
<tr>
<td>Motor skills</td>
<td>( t_{51.3} = -2.25 )</td>
<td>.029</td>
</tr>
<tr>
<td>Number of cognitive impairments</td>
<td>( r_{Spearman} = .16 )</td>
<td>.021</td>
</tr>
<tr>
<td>Predictor</td>
<td>Test value</td>
<td>$p$</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Two-year follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive function</td>
<td>$t_{46.1} = -1.74$</td>
<td>.089</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>$t_{49.2} = -3.19$</td>
<td>.003</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>$t_{42.6} = -2.13$</td>
<td>.039</td>
</tr>
<tr>
<td>Working memory</td>
<td>$t_{164} = -3.33$</td>
<td>.001</td>
</tr>
<tr>
<td>Language</td>
<td>$t_{164} = -2.36$</td>
<td>.019</td>
</tr>
<tr>
<td>Visuospatial and construction skills</td>
<td>$t_{23.1} = -2.18$</td>
<td>.040</td>
</tr>
<tr>
<td>Motor skills</td>
<td>$t_{44.4} = -2.96$</td>
<td>.005</td>
</tr>
<tr>
<td>Number of cognitive impairments</td>
<td>$r_{Spearman} = .19$</td>
<td>.009</td>
</tr>
<tr>
<td><strong>Mood state, apathy and fatigue (POMS$^{c}$)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>$r_{Spearman} = .13$</td>
<td>.059</td>
</tr>
<tr>
<td>Six-month follow-up</td>
<td>$r_{Spearman} = .18$</td>
<td>.016</td>
</tr>
<tr>
<td>Two-year follow-up</td>
<td>$r_{Spearman} = .17$</td>
<td>.033</td>
</tr>
</tbody>
</table>

$^a$National Institutes of Health Stroke Scale; $^b$Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification scheme; $^c$Profile of Mood States questionnaire, at baseline a shortened 10-item version, at follow-ups the full 30-item version was used.
Tables 4A-C present the multivariate models of income supplement use, with one model corresponding to each set of cognitive data (baseline [Table 4A], six-month follow-up [Table 4B], and two-year follow-up [Table 4C]). Prior use of income supplements undercut the need for additional post-stroke income supplementation. Expectedly, prior use of income supplements had a strong negative association with the use of stroke-related income supplements in all three models. In each model, the presence of atrial fibrillation and number of cognitive impairments were the only significant health-related predictors of income supplement use. In the first model, which included data from the baseline neuropsychological assessment, the presence of atrial fibrillation reduced the probability (hazard in survival models) of terminating stroke-related income supplement use at a given time within the first three years after stroke by 43 % (hazard ratio \(HR = .57, 95\% CI = .36-.91, p = .017\)). With each additional cognitive impairment, the probability of terminating income supplement use was reduced by 26 % \((HR = .77, 95\% CI = .68-.89, p < .001)\). In the second model, which included cognitive impairment data from patients at the six-month follow-up, the presence of atrial fibrillation reduced the probability of terminating income supplement use by 46 % \((HR = .54, 95\% CI = .31-.93, p = .027)\), and each additional cognitive impairment reduced the probability by 18 % \((HR = .82, 95\% CI = .69-.98, p = .026)\). In the last model, which included cognitive impairment data from the two-year follow-up, the presence of atrial fibrillation reduced the probability of terminating income supplements by 54 % \((HR = .46, 95\% CI = .24-.90, p = .023)\), with another 19 % reduction for each additional cognitive impairment \((HR = .81, 95\% CI = .66-.99, p = .040)\).
**Tables 4A-C.** Cox models of stroke-related income supplements use during the first three years after stroke in a cohort of working-aged stroke survivors (N = 230). Predictor lists are based on significant univariate associations with the outcome.

### A. Model with baseline cognitive data

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplement use before the stroke(^a)</td>
<td>3.66</td>
<td>2.56-5.24</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>.57</td>
<td>.36-.91</td>
<td>.017</td>
</tr>
<tr>
<td>Stroke severity (NIHSS(^b))</td>
<td>1.00</td>
<td>.90-1.10</td>
<td>.954</td>
</tr>
<tr>
<td>Functional independence (Barthel Index)</td>
<td>1.11</td>
<td>1.00-1.03</td>
<td>.064</td>
</tr>
<tr>
<td>Lesion size (largest diameter in CT(^c) / MRI(^d))</td>
<td>.87</td>
<td>.73-1.04</td>
<td>.124</td>
</tr>
<tr>
<td>Number of cognitive impairments</td>
<td>.77</td>
<td>.68-0.89</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

### B. Model with six-month follow-up cognitive and mood state, apathy and fatigue data

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplement use before the stroke(^a)</td>
<td>3.39</td>
<td>2.22-5.19</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>.54</td>
<td>.31-.93</td>
<td>.027</td>
</tr>
<tr>
<td>Stroke severity (NIHSS(^b))</td>
<td>.95</td>
<td>.85-1.07</td>
<td>.417</td>
</tr>
<tr>
<td>Functional independence (Barthel Index)</td>
<td>1.02</td>
<td>1.00-1.04</td>
<td>.070</td>
</tr>
<tr>
<td>Lesion size (largest diameter in CT(^c) / MRI(^d))</td>
<td>.88</td>
<td>.73-1.08</td>
<td>.228</td>
</tr>
<tr>
<td>Number of cognitive impairments</td>
<td>.82</td>
<td>.69-.98</td>
<td>.026</td>
</tr>
<tr>
<td>Mood state, apathy and fatigue (POMS(^e))</td>
<td>1.00</td>
<td>.99-1.01</td>
<td>.714</td>
</tr>
</tbody>
</table>
C. Model with two-year follow-up cognitive and mood state, apathy and fatigue data

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplement use before the stroke(^a)</td>
<td>2.93</td>
<td>1.83-4.68</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>.46</td>
<td>.24-0.90</td>
<td>.023</td>
</tr>
<tr>
<td>Stroke severity (NIHSS(^b))</td>
<td>.92</td>
<td>.81-1.05</td>
<td>.235</td>
</tr>
<tr>
<td>Functional independence (Barthel Index)</td>
<td>1.02</td>
<td>1.00-1.04</td>
<td>.076</td>
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<tr>
<td>Lesion size (largest diameter in CT(^c) / MRI(^d))</td>
<td>.89</td>
<td>.70-1.13</td>
<td>.343</td>
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<tr>
<td>Number of cognitive impairments</td>
<td>.81</td>
<td>.66-.99</td>
<td>.040</td>
</tr>
<tr>
<td>Mood state, apathy and fatigue (POMS(^e))</td>
<td>1.00</td>
<td>0.99-1.00</td>
<td>0.481</td>
</tr>
</tbody>
</table>

\(^a\)Supplement use before the stroke was based on combined registry and questionnaire data and included information about age- and disability-based benefits, sick-leave allowances, and unemployment funds granted to the patients; \(^b\)National Institutes of Health Stroke Scale, measured at discharge from acute care; \(^c\)Computed tomography; \(^d\)Magnetic resonance imaging; \(^e\)Profile of Mood States questionnaire
5 Discussion

5.1 Key results

The presented set of studies aimed to clarify the role of cognitive impairments in patients’ ability to return to their productive activities after a stroke. More specifically, Study I aimed to describe the parallels of post-stroke cognitive impairments and clinical severity of stroke, and Study II aimed to model predictors of post-stroke vocational outcome. In Study III, a novel method to explore post-stroke productivity beyond paid work was introduced by modelling the use of stroke-related income supplements.

In Study I, clinical severity of stroke as detected by NIHSS proved alarmingly insensitive to stroke patients’ cognitive impairments, despite the strictly conservative definition of cognitive impairments used in the study. Almost half of neurologically intact patients appeared to have clinically relevant cognitive impairments. Even after controlling for the effects of vascular risk factors, silent infarcts, leukoaraiosis and mood state, no NIHSS cut-off scores were found that would even tentatively predict intact cognition.

In Study II, the baseline cognitive severity of stroke reliably and most effectively predicted the inability to return to work six months after a stroke, taking into account various factors affecting return to work. Six months after the stroke, 41% of the patients had managed to return to their former employment. This was the first study to apply a thorough neuropsychological assessment together with other relevant health-related and health-unrelated factors to model post-stroke return to work. In the model, each cognitive impairment a patient exhibited within the first weeks after the stroke more than doubled the later risk of inability to work.

In Study III, stroke-related income supplement use data was modelled as a novel, indirect indicator of productivity losses among the whole cohort of patients irrespective of premorbid occupational status. Patients received on average of 12 months specifically stroke-related income supplements. As key results, atrial fibrillation was the most effective health-related, and cognitive
impairments the most effective stroke-related predictor of income supplement use. The study introduces one of the first attempts to measure stroke patients’ productivity-related variation that includes but is not restricted to paid employment.

5.2 Limitations

The following aspects of the study methodology should be weighed in order to interpret and evaluate the results presented here.

It was attempted to recruit as many participants as possible from a consecutive series of patients. Despite efforts, consecutive enrolment failed in 63 patients, which creates a possibility of bias in the inclusion process. The sample size was determined in advance to enable answering the research questions. However, the sample size was relatively modest for analysing complex multifactorial phenomena, especially for the controls. Furthermore, dissimilarity of sample sizes between the patients and the controls weakens the representativeness of the control data, although the two groups were similar with regard to distributions of sex, age and education.

This study was able to utilize only brain imaging available in standard clinical practice. Diagnosing ischaemic stroke can be based on clinical features even if ischemia does appear in acute CT. Only some of the patients without CT findings are referred to MRI, as it is not always a prerequisite for adequate treatment planning in the acute setting. As a consequence, every fifth patient in this study was diagnosed in the absence of imaging findings. This might potentially heighten the risk of diagnosing stroke-mimics as strokes and to a minor extent exaggerate the good recovery of this working-aged study sample compared to the general stroke population. For the main arguments of the study, however, regarding the sensitivity and significance of cognitive impairments to stroke outcome, the lack of systematic MRI for every patient has little effect.

Neuropsychological patient studies would benefit from accurate data about the patients’ premorbid cognitive state. In this study, the issue was addressed
with a carefully collected control group and by stressing sufficiently conservative and clinically relevant definition of cognitive impairments. These remedies certainly do not solve the issue entirely. Without exact data on premorbid cognitive performance, the descriptions of post stroke cognitive impairments remain estimates, at best. Sources of potential bias are found in both ends of the patient group’s cognitive performance: in excessive interpretation of weak performance as stroke-related cognitive impairments, and in underestimation of stroke-related cognitive impairments in those patients with the highest premorbid cognitive capacity.

The timing of the baseline neuropsychological assessment was balanced to minimise the possible effect of changing acute conditions, such as cerebral oedema and intracerebral pressure. However, these factors were not explicitly controlled for, which can potentially lead to an overestimation of baseline cognitive impairments. Considering the precautions taken in the timing of baseline neuropsychological assessments, the consistency of neuropsychological findings during the entire two-year follow-up, and the predictive power of the baseline cognitive impairments, the potential bias caused by these fluctuating acute phase conditions seem diminutive.

An administered but totally failed test was scored as poor performance. This decision helped in consecutive patient enrolment and enabled including some patients with very severely disabling conditions such as aphasia. However, scoring an administered but totally failed test as poor performance potentially inflates the risk of incurring a type I error in encoding other cognitive domains than the truly impaired ones as defective. For example, if a patient also failed a test other than language-related tests because of their aphasia, the patient was more likely to also have other domains scored as defective irrespective of whether the patient truly had any other cognitive impairments besides aphasia. Therefore, the reported prevalence rates of the domain-specific cognitive impairments might theoretically be marginally inflated. The prevalences of post-stroke cognitive impairments reported here are, however, relatively conservative and do not suggest this type of distortion in the results.
Patients’ own conceptions of why they have not returned to work would help the interpretation of the results in Study II. Unfortunately the question could not be fully answered.

Regarding Study III, 55 patients did not grant permission to retrieve registry data on income supplements. Compared to those 175 patients who granted access to their registry data, these 55 refusers exhibited lower education levels and higher NIHSS scores at hospital admission and they were provided shorter periods of income supplements. Potentially, this could indicate a source of systematic bias leading to minor inaccuracy in the analysis of income supplement data. However, the questionnaire data used to impute missing registry data were identical to the registry data for the patients with both registry and questionnaire data thus supporting accuracy of the income supplement data.

5.3 Interpretation

The prevalence of cognitive impairments in the first weeks after stroke is found to be above 70 %, and within the first three months 50-90 % (Gottesman & Hillis, 2010). Found prevalences depend on the sample, the timing of the assessments and the definition of cognitive impairments. In this fairly young stroke cohort, cognitive impairments were defined by mimicking clinical decision-making, resulting in prevalences of 57 % within the first weeks, 47 % at the six-month follow-up, and 44 % at the two-year follow-up. Impairments in executive functions and psychomotor speed were the most prevalent cognitive impairments from the baseline through follow-up. Rare reports on even longer-term follow-up suggest these impairments will be enduring (Schaapsmeerders et al., 2013).

These clinically significant cognitive impairments are at risk of being masked by otherwise good clinical and functional recovery and remaining unnoticed. In Study I, 41 % of clinically intact patients had cognitive impairments that could not be accounted for by confounding factors. Recently, Jokinen et al. (2015), (see also Wong & Mok, 2015), made essentially the same observation by contrasting the prevalence of cognitive impairments in a general stroke cohort...
with functional outcome measured with the modified Rankin Scale (mRS) (van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988). Consistent with the results of Study I, Jokinen et al found that cognitive impairments were common even after successful clinical recovery.

Repeated neuropsychological assessments during the two-year follow-up period allow comparing the usefulness of cognitive data gathered at baseline and later on. Importantly, post-stroke cognitive impairments could be reliably detected instantaneously after the stabilization of the acute phase. Therefore, given the critical period of heightened plasticity after stroke (Jenkins & Merzenich, 1987; Kleim & Jones, 2008; Musicco et al., 2003; Salter et al., 2006), the early timing of neuropsychological assessments has an indispensable benefit over any later timing. Late phase assessments for sure can provide coherent and reliable information and serve multiple purposes in patient care. However, only a balanced early timing of a neuropsychological assessment enables utilizing cognitive data during this transient period of most efficient recovery and rehabilitation.

According to Study II, early neuropsychological assessments can also serve stroke treatment in the prediction of vocational outcome. This finding is a valuable addition to previous research, which has emphasised baseline cognitive impairments as predictors of the later cognitive (Nys, van Zandvoort, de Kort, van der Worp et al., 2005) and functional outcomes (Barker-Collo & Feigin, 2006; Feigin et al., 2008) and quality of life after stroke (Hochstenbach et al., 2001; Nys et al., 2006).

The association of both the clinical (NIHSS) severity of stroke and functional impairments (Barthel Index) with the vocational outcome was clear in Study II in conjunction with previous studies (Busch, Coshall, Heuschmann, McKevitt, & Wolfe, 2009; Neau et al., 1998). Study II also replicated previous research suggesting other than health-related factors, such as age, education and type of work, to affect the post-stroke vocational outcome (Howard et al., 1985; Tanaka et al., 2011). Study II was the first to adjust the analysis of these diverse factors for the effect of cognitive impairments, which led to the proposal that the
cognitive severity of stroke was an even more important predictor. Returning to work has been proposed as a global outcome measure that assesses the efficacy of multidisciplinary treatment strategies for any working individual who develops a stroke (Singhal & Lo, 2014). Should return to work claim such a linchpin role as an outcome measure of stroke in the working-aged, the findings of Study II set early neuropsychological assessments as an essential part of multidisciplinary post-stroke treatment planning.

The inability of many working-aged stroke patients to return to work is a major contributor to stroke-related productivity losses. As an outcome measure, however, returning to work remains potentially insufficient. It excludes an evident portion of the study population: those outside of the workforce already at the time of their strokes. Yet there are massive socio-economic discrepancies in stroke incidence, treatment and outcome (Addo et al., 2012), income level being inversely related to the risk of stroke. Arguably, the need to describe the indirect consequences of stroke without excluding some of those potentially suffering harder from stroke is evident. Study III presented one of the first attempts to measure and predict stroke-related productivity losses including but not restricted to employment. In study III, stroke-related income supplement use was introduced as a novel parameter to evaluate the productivity-related variation among working-aged stroke patients without the prerequisite of employment. The idea was that the use of income supplements, when specifically granted on the basis of the stroke, could be taken as a sign of productivity-related disability in both employed and others as well. In the study, approximately every third patient received disability-based benefits at the three-year follow-up. This observation is in concordance with the post-stroke unemployment data from Netherlands (Maaijwee et al., 2014). Unlike in the Maaijwee et al study, Study III utilized multiple health-related factors in the prediction of disability payment usage. As a result, the use of stroke-related income supplements was most effectively predicted by atrial fibrillation and cognitive impairment, both well-known effectors of stroke outcome.

Atrial fibrillation, which is under-diagnosed, undertreated, and associated with large strokes and increased early mortality, is a leading cause of stroke
(Lamassa et al., 2001). That atrial fibrillation appeared also as the strongest health-related predictor of stroke-related income supplement use, seems to be a logical continuum. Yet the finding is noteworthy considering that incidence of atrial fibrillation increases with age (Wolf, Abbott, & Kannel, 1991) and that in this cohort of working-aged stroke survivors the prevalence of atrial fibrillation was as low as 11% (all cardiac aetiologies 21%).

Several factors relating to the incident stroke were compared in the prediction of income supplement usage, including clinical severity, functional impairment, and lesion characteristics. From the baseline through the follow-up, the most effective stroke-related effector of disability payment use was cognitive impairment, while the effectors remained multifactorial. Thus, expanding the evaluation of stroke-related productivity losses from the employed (Study II) to the whole cohort (Study III) did not alter the central role of cognitive impairments to the indirect costs of stroke, nor did it change the need for a multifactorial account.

The findings of Study I-III bear relevance to both understanding the global burden of stroke and treatment planning. Encouragingly good clinical and functional recovery commonly seen after contemporary acute stroke treatment has not stopped the accumulation of socio-economic burden of stroke (Brown et al., 2006; Feigin et al., 2015). Aging population is the most important factor behind the increase, but not the only one (Feigin et al., 2015). The incidence of stroke among the younger population in the middle of their most demanding and productive years is growing (Krishnamurthi et al., 2015). As cognitive impairments seem to mediate post-stroke productivity losses, the growing understanding of post-stroke cognitive impairments can help in treating the accumulation of stroke burden.
5.4 Generalizability

The patients in this study were working-aged (18–65 years) and suffering their first-ever ischaemic stroke. The majority of strokes occur in elderly patients, and every sixth stroke is recurring (Aivoinfarkti. Cerebral infarction [stroke]: Current Care Guidelines Abstract, 2011). In what sense then can studying working-aged patients inform understanding of stroke in general? First, focusing on these relatively young stroke survivors suffering their first-ever stroke supported the aim to minimize the bias caused by potential pre-existing cognitive impairment, from which it is generally impossible to gather explicit knowledge in a clinical setting. Second, stroke in the working-aged population disproportionally raises the total socio-economic burden of stroke (Brown et al., 2006). Arguably the working-aged subgroup bears relevance to stroke research in general.

Being relatively young, suffering their first-ever stroke, and receiving modern acute stroke care, the cohort’s favourable clinical and functional outcome was expected. Yet the small amount of very severely injured patients in the sample requires evaluation of the study setting and success in the consecutive recruitment of patients. During recruitment, six patients were excluded because they were too severely injured to complete the neuropsychological assessment. These exclusions certainly cause a slight underestimation of the median NIHSS score and Barthel Index for the purpose of generalizing the results to the general stroke population. However, as one of the main arguments of this set of studies is that clinically relevant cognitive impairments are relatively prevalent of among patients with less severe strokes, the good clinical and functional recoveries are not an argument against the generalizability of the results. In fact, due to the good clinical and functional outcomes, this working-age cohort presents an essential stroke subpopulation at risk of suffering from non-detected cognitive impairments.

The successful clinical and functional recovery of the cohort also relates to the generalizability of the results regarding the multivariate model of return to
work after stroke, where cognitive impairments most effectively predicted the return to work after stroke. The mild clinical impairments of the cohort raise the question of whether the predictive model would emphasize different aspects of stroke severity in a cohort with more prominent clinical impairments. This concern is emphasized given that 21 dropouts from the six-month follow-up exhibited higher median NIHSS scores than the participants of the six-month follow-up. As a sum score of the multiple gross neurological impairments, the NIHSS captures many of the obvious hindrances of working life. In a cohort with frequent gross neurological impairments, a high NIHSS score would certainly offer a powerful estimate for the vocational outcome. This consecutive cohort was designed to be representative of working-aged patients with their first-ever stroke who have received high standard acute stroke treatment. When leaving acute care, 61% of the patients in the present study had a NIHSS score of zero or one. Nevertheless, the patients’ cognitive impairments were disabling and frequent enough to explain the rather adverse return-to-work rate. Perhaps symptomatically, those dropouts from the six-month follow-up, with higher baseline median NIHSS scores, also had more frequent impairments in psychomotor speed. Indeed, in many cases, the cognitive impairments seem to be the primary health-related determinant of the vocational outcome, and gross neurological impairments are insensitive to more fine-grained yet debilitating cognitive impairments (Gottesman et al., 2010).

Merely 41% of the patients previously working full time in paid employment outside the house had returned to work six months after the stroke. The post-stroke return-to-work rates vary noticeably among different studies due to different definitions of work (Daniel et al., 2009; Treger et al., 2007). Studies defining work similarly as paid employment outside the house typically report approximately half of the patients returning to work (Daniel et al., 2009). The lower return-to-work rate of this study could possibly reflect between-country differences, for example, in the availability and duration of disability-based income supplements.

External validity of the results depends heavily on the clinical relevance of cognitive impairment definitions. A thorough neuropsychological assessment
was used to collect cognitive data. Each cognitive domain was measured with three separate tests, and defective test performance was defined in relation to carefully collected control group performance. To denote impairment, at least two out of the three within-domain test scores were required to be defective. This method of chasing a repeating pattern of defective test performance instead of single deviant test scores mimics clinical neuropsychological decision making and significantly narrows the criteria for a defective performance. As a consequence of this conservative method, prevalence of baseline cognitive impairments was somewhat lower (57 %) than previously reported (approximately 70 %) (Gottesman & Hillis, 2010).

The structures of healthcare systems, the levels of income supplementation and the durations of these benefits vary significantly across countries. The present study was conducted in Finland, which to date has had a relatively strong socio-economic support system. Thus, to assess whether the results are applicable and relevant to other countries with different social security support systems, some of the assumptions made in this study must be explained and delineated to indicate what has and has not been measured.

First, the generalizability of the Study III’s results relies on the assumption that many, though not all, societies have a social security programme that contains an economic support mechanism for severe and enduring illnesses such as stroke. Second, the generalizability of the results relies on the assumption that there is measurable variation within a disability-based benefit programme, that is, not all benefactors obtain the same benefits irrespective of their condition. The variation between the support systems of different societies does not threaten the generalizability of the approach taken. As long as measurable variation within a disability-based benefit programme exists, evaluating stroke-related changes in income supplement use can provide a complementary perspective on stroke-related productivity. The expenses of disability-based benefits apparently vary both between and within countries because of varying income levels and many other factors. Rather than measuring the amount of money spent on stroke patients, Study III focused on factors that could predict differences in the length of time that the patients used
the income supplements. Obviously, the duration of these benefits varies between countries. In this Finnish cohort of working-aged patients who experienced a first-ever ischaemic stroke, stroke led to income supplement use for a mean of 11 months. In other countries, the mean time of stroke-related supplement use is likely to be different, but the variation can be measured and predicted with significant effectors.

Study III results are not generalizable in the sense that the study could not be replicated in countries without a social security system that includes a mechanism to provide disability-based support. However, the need to understand stroke-related productivity losses more thoroughly than merely by the inability to work is pressing, irrespective of the social security policy at hand. Therefore, the results of Study III can still be relevant to societies without a disability support programme.

5.5 Concluding remarks

Productivity losses are crucial to the huge socio-economic burden of stroke. Cognitive impairments’ central role in mediating adverse stroke outcome is emerging and elucidating. Nevertheless, stroke research covering productivity and cognitive impairments are sparse. The aim of this study was to describe post-stroke cognitive impairments in terms of productivity-related recovery. The main findings were that clinically significant cognitive impairments were alarmingly common even among neurologically well-recovered patients, that cognitive impairments most effectively predicted return to work after stroke, and that together with atrial fibrillation, cognitive impairments also effectively predicted stroke-related income supplement use.

There appears to be no safe limit for assuming intact cognition in stroke patients based on clinical recovery, a finding that has recently been replicated (Jokinen et al., 2015). Given the established possibilities to treat cognitive impairments after stroke (Cicerone et al., 2011) and the significance of cognitive impairments to stroke outcome (Barker-Collo & Feigin, 2006; Feigin et al., 2008; Gottesman & Hillis, 2010; Hochstenbach et al., 2001; Jaillard et al., 2009; Kotila et al., 1984; Nys, van Zandvoort, de Kort, van der Worp et al.,
2005; Nys et al., 2006; Treger et al., 2007; Wiberg, Kilander, Sundstrom, Byberg, & Lind, 2012; Wozniak & Kittner, 2002), the benefits of early neuropsychological assessments to treatment planning are emphasised. Finally, according to Studies II-III, effectors of post-stroke productivity are multifactorial by nature and strongly associated with cognitive impairments.
6 References


